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Original article

Reduced incidence of Type 1 diabetes and Type 2 diabetes in systemic sclerosis: A nationwide cohort study

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ABSTRACT

Objectives: The purpose of this study is to investigate whether systemic sclerosis is a risk factor for diabetes.
Methods: From Taiwan's National Health Insurance Research Database and Registry of Catastrophic Illness database, we enrolled patients with systemic sclerosis and controls. Each systemic sclerosis patient was matched to at most three controls by sex, age, month and year of first diagnosis. Standardized incidence ratio (SIR) of diabetes in systemic sclerosis patients, and 95% confidence interval (95% CI) were calculated. Cox hazard regression was used to calculate the hazard ratio (HR).
Results: A total of 2671 patients with systemic sclerosis and 7769 controls were enrolled. Patients with systemic sclerosis had decreased type 1 diabetes (SIR: 0.18, 95% CI = 0.04–0.82). In female groups, systemic sclerosis patients also had lower rates of incident type 1 diabetes (SIR: 0.21, 95% CI = 0.05–0.95). Male and female patients with systemic sclerosis both had lower rates of incident type 2 diabetes (SIR: 0.46, 95% CI = 0.29–0.72; SIR: 0.41, 95% CI = 0.33–0.51, respectively). Systemic sclerosis patients had decreased type 1 diabetes and type 2 diabetes (HR: 0.18, 95% CI = 0.04–0.74; HR: 0.42, 95% CI = 0.36–0.50, respectively) after adjusting for age and sex.
Conclusions: The results clearly showed that patients with systemic sclerosis had lower incidence of type 1 diabetes and type 2 diabetes compared to control subjects.

1. Introduction

Systemic sclerosis is characterized by Raynaud's phenomenon and pulmonary hypertension caused by vascular abnormalities [1]. It is divided into subtypes: limited and diffuse forms, and is associated with various autoantibodies such as: anticentromere, anti-topoisomerase I and/or anti-RNA polymerase III antibodies.

There are many comorbidities found in systemic sclerosis. Systemic sclerosis can be associated with myocardial infarction, stroke, and peripheral vascular disease [1]. However, little is known about the relationship between systemic sclerosis and diabetes. Traditionally, diabetes encompasses type 1 diabetes and type 2 diabetes. Type 1 diabetes is characterized by autoimmune destruction of the insulin-secreting beta cells in the pancreas, with a substantial proportion diagnosed after the age of 40 [2]. Type 2 diabetes is associated with insulin resistance [3].

Past studies showed that diabetes was associated with increased incidence of myocardial infarction and stroke [3], similar to systemic sclerosis [1]. Furthermore, in patients with systemic sclerosis, diabetes was associated with increased overall mortality and cardiovascular mortality independent of systemic sclerosis [4]. Although past studies showed lower prevalence of diabetes in systemic sclerosis [5], it was not known whether the incidence of diabetes increased or decreased in systemic sclerosis patients.

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Additionally, whether age or sex is correlated with the incidence of diabetes needs further clarification. Understanding the incidence of diabetes in systemic sclerosis would provide informative information to clinicians as to whether screening for diabetes in systemic sclerosis population is useful. Thus we conducted this study to evaluate the incidence of diabetes in systemic sclerosis.

2. Methods

In Taiwan, the National Health Insurance (NHI) program was launched in 1995, covering 99% of the total population [6]. The information from the NHI database included diagnosis of patients, dates of doctor visits, sex, and ages of patients. Numerous studies have utilized the NHI database to survey the incidence of comorbidities in various diseases, including systemic sclerosis and diabetes – including type 1 diabetes and type 2 diabetes [6–9]. To guarantee the precision of the claim data, the Bureau of NHI (BNHI) performs expert reviews on a random sample of every 50–100 ambulatory and in-patient claims in each hospital and clinic quarterly. False reports of diagnosis yield a severe penalty from the BNHI [8]. The objectives of this study were to investigate the incidence of type 1 diabetes and type 2 diabetes in systemic sclerosis patients in Taiwan, based on the NHI data from January 1998 to December 2010.

2.1. Source population and data

We conducted a retrospective cohort study to investigate the association between systemic sclerosis and diabetes based on the NHI medical claims database. The NHI medical claims database, including hospital inpatient care, outpatient visits, ambulatory care, and dental services, is managed by Taiwan's National Health Research Institutes (NHRI). The NHRI offered 1,000,000 random subjects from the National Health Insurance Research Database (NHIRD) for this study, representing about five percent of Taiwan's population. There were no differences in age and sex distribution [8] between this population and the entire population in Taiwan. We obtained a longitudinal cohort from the NHIRD from January 1, 1998, to December 31, 2010. Another database acquired from the NHRI was the Registry of Catastrophic Illness database consisting of information of 23 million Taiwanese patients. As per the scheme, insured persons with major diseases, including systemic sclerosis and type 1 diabetes, could apply for a catastrophic illness certificate, which exempted the individual from co-payment. To be registered in Registry of Catastrophic Illness database for systemic sclerosis, an individual must meet the 1980 American College of Rheumatology systemic sclerosis classification criteria. To be registered in the Catastrophic Illness database for type 1 diabetes, an individual must have relevant medical records (including fasting or glucagon-stimulated C-peptide level, anti-glutamic acid decarboxylase antibody level, and history of ketoacidosis). Applications for catastrophic illness certificates were validated by respective specialists based on a careful examination of the medical records as well as laboratory and imaging studies. Because NHRI used encrypted identification number in these two databases, it is impossible to identify individuals. Thus an ethical approval for analysis of the database was exempted by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20140007).

2.2. Study sample

NHI database diagnosis coding follows the International Classification of Diseases, Ninth Revision (ICD-9), Clinical Modification diagnostic criteria. We used the Registry of Catastrophic Illness database to include patients in Taiwan with newly diagnosed systemic sclerosis (ICD-9:7101) after the age of 20 during the period of January 1, 1998 to December 31, 2010. Patients with diabetes (ICD-9:250) [8] diagnosed before systemic sclerosis were excluded. Patients with systemic sclerosis diagnosed before January 1, 1998 were excluded to ensure that the baseline population of systemic sclerosis was actually newly diagnosed after enrollment, allowing a 3-year run-in period. We used NHIRD to collect the control group without diagnosis of systemic sclerosis (ICD-9: 7101). Each systemic sclerosis patient was matched to one to three non-systemic sclerosis controls by gender, age, and month and year of first diagnosis at enrollment. Patients with diabetes (ICD-9:250) diagnosed before the matching day were excluded. This matching was to ensure that there were no difference in sex, ages, and follow-up time between study subjects and controls. We identified patients with type 1 diabetes (ICD-9:250.x1 or 250.x3 registered in the Registry of Catastrophic Illness database) and type 2 diabetes (ICD-9:250, excluding 250.x1, 250.x3) noted during the follow-up. Earlier studies also used this approach to identify patients with systemic sclerosis and diabetes – including type 1 diabetes and type 2 diabetes [3,6–9]. This approach has been validated, with 93.2% sensitivity and 92.3% positive predictive value (PPV) for diabetes [6], 98.3% PPV for type 1 diabetes [9].

Enrollment started on the date of first diagnosis of systemic sclerosis in the systemic sclerosis group and on the same day in the matched control group. Follow-up ended on the day of diagnosis of diabetes (or type 1 diabetes or type 2 diabetes for the analysis of type 1 diabetes and type 2 diabetes) identified as the presence of related ICD-9, death, transfer out, or the end of 2010. Because diabetes mellitus has an insidious onset and may not be diagnosed immediately, we subtracted 1 year from the date of the clinical diagnosis for diabetes, as well as the sampled date of matching subjects, as the end date [10]. The follow-up period was calculated from the cohort enrollment date to the end date. If follow-up was less than 1 year, patients and matching subjects would be excluded due to inadequate duration to assess long-term effects of systemic sclerosis [10].

2.3. The incidence of diabetes, Type 1 diabetes, Type 2 diabetes, and Standardized Incidence Ratio (SIR)

We evaluated the incidence of diabetes – type 1 and type 2 – in patients with systemic sclerosis and control subjects, and calculated the standardized incidence ratio (SIR), which is ratio of incident diabetes – type 1 and type 2 – in patients with systemic sclerosis as compared to the controls [11].

2.4. Statistical analyses

Cox hazard regression was used to calculate the hazard ratio (HR) and 95% confidence intervals (95% CI) for incident diabetes – type 1 and type 2 – in patients with systemic sclerosis compared to the controls after controlling age and gender. We used log-rank tests to compare cumulative hazard rates between different patient groups. All statistical operations were performed using SPSS (v19.3) after mining the national records using the PERL (v5.8).

3. Results

This study included a total of 2671 patients with systemic sclerosis and 7769 controls for the period of January 1998 to December 2010. In males, the mean ages of systemic sclerosis and controls were 51.45 (± 15.41) and 52.14 (± 15.12) years, respectively (Table 1). The age distribution between systemic sclerosis and controls was not significantly different ($P > 0.05$) in males. In females, the mean ages of systemic sclerosis and controls were 48.12