Concise report

Hydroxychloroquine reduces risk of incident diabetes mellitus in lupus patients in a dose-dependent manner: a population-based cohort study

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Abstract

Objective. SLE is associated with increased risk of diabetes mellitus. Treatment for SLE requires high-dose glucocorticoids that may worsen glucose homeostasis. HCQ can reduce diabetes risk in RA. This study aimed to investigate the association of HCQ use and diabetes mellitus risk in SLE patients.

Methods. This nationwide, population-based cohort study was conducted using the Taiwan National Health Insurance Research Database. In the period 2001–10, 8628 newly diagnosed SLE patients were identified after excluding those with a previous diagnosis of RA, psoriasis or diabetes mellitus. Incidence of diabetes mellitus was identified as a new diagnostic code using a diabetes mellitus-specific medication.

Results. Two hundred and twenty-one newly diagnosed diabetes mellitus patients were identified among SLE patients (6795 had taken HCQ and 1833 had never taken HCQ), with an average follow-up period of 5.6 years. Compared with patients without HCQ treatment, the hazard ratio (HR) of diabetes mellitus in patients taking HCQ at a cumulative dose ≥129 g was reduced [HR 0.26 (95% CI 0.18, 0.37), P < 0.001]. Daily glucocorticoid ≥10 mg prednisolone-equivalent dose was associated with increased risk of developing diabetes mellitus [HR 2.47 (95% CI 1.44, 4.23), P = 0.001], which was minimized by concomitant HCQ use at a cumulative dose ≥129 g.

Conclusion. In SLE patients, the use of HCQ is associated with reduced risk of incident diabetes mellitus in a dose-dependent manner. High-dose glucocorticoids increase the risk of diabetes, which can be decreased by concomitant HCQ use.

Key words: systemic lupus erythematosus, hydroxychloroquine, glucocorticoid, diabetes.

Rheumatology key messages

- HCQ is associated with reduced incident diabetes mellitus risk in a dose-dependent manner in SLE.
- Glucocorticoid-associated diabetes mellitus in SLE patients can be ameliorated by concomitant use of HCQ.
Introduction

Increasing evidence indicates that SLE is associated with premature atherosclerosis and cardiovascular diseases [1, 2]. Although chronic inflammation has been identified as an important risk factor for cardiometabolic diseases, traditional risk factors such as diabetes mellitus, hypercholesterolaemia and hypertension also play a critical role in cardiovascular risks in patients with SLE [2, 3].

Diabetes and related complications of atherosclerotic diseases are major causes of morbidity and mortality in the general population. It is well established that chronic inflammation contributes to insulin resistance, which commonly precedes the development of diabetes mellitus [4]. Recent studies indicate that RA and psoriasis are associated with elevated risks of insulin resistance and diabetes mellitus [5]. The risks of incident diabetes mellitus are also increased in SLE patients [3]. On the other hand, traditional and biologic DMARDs are associated with reduced risk of diabetes mellitus [6].

HCQ is an antimalarial drug that is widely prescribed for the treatment of SLE and RA. Although rarely, HCQ can cause hypoglycaemia [7]. In patients with non-rheumatic type 2 diabetes mellitus, HCQ can improve glycaemic control [8], while in diabetic patients with rheumatic diseases, HCQ treatment is associated with reduced haemoglobin A1c (HbA1c) [9]. Moreover, the use of HCQ is associated with reduced fasting glucose and insulin resistance in non-diabetic women with SLE and RA [10]. Large epidemiological studies have demonstrated that HCQ therapy reduces the risk of incident diabetes mellitus in patients with RA and psoriasis [6, 11]. The reduced incident diabetes risk is related to the duration of exposure to HCQ [11].

Compared with RA or psoriasis, SLE with major organ involvement more often warrants treatment with high-dose glucocorticoids. Glucocorticoids may alter glucose metabolism and contribute to diabetes mellitus [12]. Whether HCQ treatment can reduce incident diabetes mellitus risk in SLE patients is unknown. Under the hypothesis that the use of HCQ is associated with a reduced likelihood of diabetes mellitus, this nationwide population-based study was conducted to examine the association of HCQ therapy with incident diabetes mellitus risk in SLE patients.

Methods

Study design

The data source was the National Health Insurance Research Database (NHIRD) of Taiwan covering inpatient and ambulatory care claims from 2001 to 2010. The National Health Insurance (NHI) programme of the Bureau of National Health Insurance (BNHI) covers >98% of the population in Taiwan. It utilizes a comprehensive computerized database, including all medical claims for ambulatory care services and hospitalization, and can therefore facilitate a nationwide population-based cohort study. The BNHI performs routine validation of the diagnoses by reviewing the original medical charts of all patients. The NHIRD established a registry system for catastrophic illnesses, including SLE. The completeness and accuracy of the NHI claims databases were assured by the aforementioned agencies. Because the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the Institutional Review Board.

Study cohort

This retrospective cohort study enrolled all SLE patients [International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) code 710.0] in Taiwan found in the registry for catastrophic illnesses covering the period 2001–2008. The index date for the study cohort was identified as the date of the first ambulatory care visit with a diagnosis of SLE. To identify new SLE cases, those who had an index date before 1 January 2001 were excluded. Those who were followed up for <3 years were also excluded, as well as patients with a diagnosis of RA (ICD9-CM code 741.0), psoriasis (ICD9-CM code 696) or diabetes mellitus (ICD9-CM code 250) before enrolment and those with incomplete information. The study cohort was composed of 8628 SLE patients.

Hypertension (ICD9-CM code 401–405), hyperlipidaemia (ICD9-CM code 272), stroke (ICD9-CM code 430–438), ischaemic heart disease (ICD9-CM code 410–414) and chronic kidney disease (ICD9-CM code 585) were co-morbid medical disorders. If these diagnostic codes were used in two or more ambulatory claims 12 months before the index date, they were recorded as co-morbidities. Pharmacological treatment of lupus given within 12 months after the diagnosis of SLE was included. The cumulative dose of HCQ and daily dose of prednisolone-equivalent glucocorticoids were calculated.

Study outcomes

The primary outcome was incident diabetes mellitus. The definition of diabetes mellitus required at least two diagnoses of diabetes mellitus (ICD9-CM code 250) and a new prescription of diabetes mellitus-specific medication (all insulin preparations and oral anti-diabetic drugs). All patients were followed up until the occurrence of endpoints, permanent disenrolment from NHI or the end of the study (31 December 2010), whichever came first.

Statistical analysis

To examine the unadjusted comparisons, \( \chi^2 \) test was used for categorical variables. The hazard ratio (HR) of incident diabetes mellitus was determined by the Cox proportional hazard model with 95% CI. Diabetes mellitus-free survival curves were plotted via the Kaplan–Meier method, with statistical significance examined by the log-rank test. Multivariate Cox proportional hazard models were used to identify independent factors contributing to the development of diabetes mellitus. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). All statistical tests were
two-sided, conducted at a significance level of 0.05 and reported using P-values and/or 95% CIs.

Results

Patient distribution

In all, 9485 newly identified SLE patients were eligible (supplementary Fig. S1, available at Rheumatology Online). After excluding patients with a prior history of RA (n = 245), psoriasis (n = 128), diabetes mellitus (n = 482) and those with incomplete information (n = 2), the final study cohort consisted of 8628 SLE patients.

Demographic characteristics of the SLE cohort

The total observation period for the enrolled SLE patients was 5.6 years (s.d. 2.6). The majority (88.2%) of patients were female, with an average age of 37.0 years (s.d. 14.6). Compared with patients without HCQ treatment, those using HCQ were older [48.6 years (s.d. 16.2) vs 36.7 (s.d. 14.4), P < 0.001] and a greater proportion had taken glucocorticoids (92.1% vs 72.9%, P < 0.001). The prevalence of hypertension, hyperlipidaemia, stroke and renal disease was significantly lower in those with HCQ treatment (supplementary Table S1, available at Rheumatology Online).

Effect of HCQ on preventing incident diabetes mellitus

To study the impact of drug treatment on incident diabetes mellitus, the HR for developing diabetes was examined (Table 1). The risk of incident diabetes mellitus increased with advancing age, with the highest risk among those aged >50 years [HR 8.38 (95% CI 3.78, 18.60), P < 0.001]. Compared with those who had taken a cumulative HCQ dose of <129 g, those who had taken HCQ a cumulative dose of ≥129 g had a significantly lower probability of developing diabetes mellitus (Fig. 1A). Patients with a cumulative HCQ dose of ≥129 g had the lowest HR for diabetes [HR 0.26 (95% CI 0.18, 0.37), P < 0.001]. However, patients with a cumulative HCQ dose of <129 g were not protected from developing diabetes [HR 1.13 (95% CI 0.81, 1.59), P = 0.423].

Glucocorticoid, HCQ and risk of diabetes mellitus

The risk of incident diabetes was significantly higher in SLE patients taking daily glucocorticoid ≥10 mg prednisolone-equivalent dose [HR 2.29 (95% CI 1.34, 3.93), P = 0.003] (Table 1). The use of DMARDs was not associated with diabetes mellitus risk. Patients with SLE and hypertension carried a greater risk of diabetes mellitus [HR 1.90 (95% CI 1.38, 2.63), P < 0.001] compared with those without hypertension. Ischaemic heart disease was also associated with risk of developing diabetes mellitus [HR 1.73 (95% CI 1.19, 2.51), P = 0.004].

The Kaplan–Meier survival plot revealed the different protective effects of HCQ on diabetes mellitus according to daily glucocorticoid dosage (Fig. 1B and C). Patients taking a cumulative HCQ dose <129 g and daily glucocorticoid ≥10 mg had a higher diabetes mellitus risk than those taking glucocorticoid at <10 mg (Fig. 1B). However, the high-dose glucocorticoid-associated diabetes mellitus risk was reduced in patients on cumulative HCQ ≥129 g (Fig. 1C).

The relationship between age, sex, drug treatment, co-morbidities and diabetes mellitus risk was evaluated between HCQ users with cumulative doses ≥129 g and <129 g. After adjustment for age, sex, drug treatment and co-morbidities, the HR for diabetes risk was dramatically reduced in HCQ users with a cumulative dose ≥129 g (HR range 0.10–0.41) in different age groups, in patients taking concomitant glucocorticoids or DMARDs and in those with co-morbidities (Fig. 1D).

Discussion

This is the first report of a population-based cohort study that demonstrates that HCQ use reduces the risk of diabetes in a dose-dependent manner among SLE patients. Daily glucocorticoid use of ≥10 mg prednisolone-equivalent dose increases the risk of diabetes mellitus. However, concomitant use of HCQ at a cumulative dose ≥129 g ameliorates the potential adverse effects of glucocorticoid-induced diabetes mellitus.

Lupus-associated inflammation has been associated with insulin resistance and atherosclerosis [4]. SLE patients have increased risk of developing diabetes mellitus, which is an established risk factor for cardiovascular diseases [3, 13]. Type 2 diabetes mellitus may lead to renal insufficiency and neuropathy, which can complicate the management of SLE [14]. Therefore it is essential to reduce the risk of incident diabetes mellitus in SLE patients.

Accumulating evidence has revealed that inflammation is important in the pathogenesis of type 2 diabetes mellitus [15–17]. Pro-inflammatory cytokines are associated with insulin resistance [16, 17]. In patients with non-rheumatic type 2 diabetes mellitus, HCQ has been reported to improve glycaemic control [8]. The use of HCQ and anti-TNF agents is associated with reduced diabetes mellitus risk among RA patients [6, 11], while HCQ use is also associated with improved insulin sensitivity in SLE patients [10]. However, the association of HCQ with incident diabetes mellitus risk among SLE patients has not been previously explored.

The present study demonstrates that HCQ use is associated with reduced diabetes mellitus incidence in SLE patients. Moreover, the protective effect of HCQ is dose dependent, consistent with findings of a previous study in which RA patients taking HCQ for >4 years had the lowest incident diabetes mellitus rate [11]. We demonstrate that a cumulative HCQ dose ≥129 g (200 mg/day for 1.8 years) is associated with reduced risk of developing diabetes in SLE patients.

There are substantial differences in the clinical characteristics of SLE patients with and without HCQ use. Those with HCQ use are older and have taken more glucocorticoids, MTX, SSZ and AZA, but less CYC, than those without HCQ use. Moreover, patients taking HCQ have less hypertension, hyperlipidaemia, stroke and renal disease.
The difference may reflect the discrepancy in lupus disease activity between the two groups. The higher frequency of CYC use and renal disease in those without HCQ use suggests that these patients may have more frequent lupus renal involvement. Chronic inflammation is known to be an important factor in insulin resistance [4]. Therefore those without HCQ use may be biased toward increased risk of diabetes mellitus due to disease activity. However, those with HCQ have more glucocorticoid use, which can predispose to the development of diabetes mellitus. Despite differences between the two study groups, the characteristics of the overall study cohort are representative of real-life outpatient SLE patients in Taiwan.

Glucocorticoids are the mainstay of treatment for SLE, but glucocorticoid-induced diabetes mellitus has been reported in those who had previously been normoglycaemic [12]. In RA patients, long-term glucocorticoid therapy may

### TABLE 1 Multivariate analysis for new-onset diabetes mellitus

<table>
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<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Events</th>
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<th>Incident rate of diabetes mellitus</th>
<th>HR (95% CI)</th>
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<tr>
<td>&lt;16</td>
<td>817 (9.5)</td>
<td>7</td>
<td>4704</td>
<td>1.49</td>
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<td>16–50</td>
<td>6432 (74.5)</td>
<td>113</td>
<td>37160</td>
<td>3.04</td>
<td>2.41 (1.12, 5.21)</td>
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<td>≥50</td>
<td>1379 (16.0)</td>
<td>101</td>
<td>6634</td>
<td>15.22</td>
<td>8.38 (3.78, 18.60)</td>
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<td>Women</td>
<td>7609 (88.2)</td>
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<td>43140</td>
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<td>Men</td>
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<td>5359</td>
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<td>1–129</td>
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<td>≥129</td>
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<td>10.28</td>
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<td>&lt;5</td>
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<td>2345</td>
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<td>240 (2.8)</td>
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<td>40825</td>
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<td>Yes</td>
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<td>7673</td>
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Per 1000 person-years. FT: follow-up time; HR: hazard ratio; ref: reference.
worsen pre-existing diabetes and predispose to diabetes mellitus [18]. The use of high-dose glucocorticoids is associated with diabetes mellitus development in SLE patients [19]. In this study, average daily glucocorticoid 510 mg prednisolone-equivalent dose is associated with increased diabetes risk, which can be reduced by HCQ use if the cumulative dose is 129 g.

This study has three advantages. First, it is a nationwide, population-based study on incident diabetes mellitus that uses an administrative database, thus avoiding selection bias. Second, the NHIRD provides complete information on outpatient and inpatient visits and prescriptions, which prevents underreporting of medical visits and pharmacological treatment [20]. Third, >98% of Taiwan’s residents are of Chinese Han ethnicity. The homogeneous population eliminates the confounding effects of ethnicity.

However, this study also has several limitations, which are mainly derived from the claims data per se. First, the lupus disease severity and laboratory data of HCQ users and non-users are unknown. Confounding by indication may exist and may account for differences in outcomes. This also prevents studies on the relationship between lupus activity and incident diabetes mellitus risk. Besides, only treatment data of the first year were recorded. Disease relapse, disease severity and the use of other DMARDs in the prolonged follow-up period may have impacted on incident diabetes. However, as

Comparisons of the probability of SLE patients developing diabetes mellitus over 10 years according to (A) cumulative HCQ dosage (in g) and daily glucocorticoid dosage relative to a cumulative HCQ dosage (B) <129 g and (C) 129 g using the Kaplan–Meier method. (D) Multivariate stratified analyses of the association between HCQ dose and diabetes mellitus risk. Among SLE patients, use of HCQ at a dose 129 g was associated with reduced risk of incident diabetes mellitus in nearly all analyses (stratified by age, sex, glucocorticoid dosage, DMARD use and co-morbidities).
illustrated in Fig. 1A, we believe that much of the excess diabetic risk arises early in the first-year period of HCQ use and remains significant over time. After adjustments for pharmacological treatment and co-morbidities, HCQ use remains significantly associated with reduced diabetes mellitus incidence. Second, there is a lack of information on lifestyle, BMI and family history, which may also influence the risk of developing diabetes mellitus.

In conclusion, this nationwide, population-based study reveals that HCQ use is associated with reduced incident diabetes mellitus risk in a dose-dependent manner among patients with SLE. Glucocorticoid-induced diabetes mellitus can be ameliorated by concomitant use of HCQ at a cumulative dose $\geq 129$ g.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

References


