Diabetes Epidemiology and Management 8 (2022) 100089

Contents lists available at ScienceDirect

Diabetes Epidemiology and Management

journal homepage: www.elsevier.com

Original article

Hydroxychloroquine lowers the risk for Diabetes Mellitus in patients with Systemic Lupus Erythematosus

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ARTICLE INFO

Article History:
Received 14 April 2022
Revised 28 May 2022
Accepted 30 May 2022
Available online 31 May 2022

ABSTRACT

Background: Previous literature suggests a lower prevalence of diabetes mellitus (DM) in patients with systemic lupus erythematosus (SLE).
Study question: We aimed to investigate the impact of hydroxychloroquine (HCQ) on the risk of DM in patients with SLE.
Study design: We queried The TriNetX database for all patients aged >18 years diagnosed with SLE from January 1, 2000, until January 1, 2021. We identified patients with SLE using disease−specific International Classification of Diseases, Tenth Revision (ICD-10) diagnosis code (M32). At the time of enrollment, we excluded all patients who were diagnosed with diabetes mellitus (ICD-10 code: E08-E13) either prior to or at the initial visit.
Measures and outcomes: Patients were classified into two groups according to treatment with HCQ. The primary objective was to compare the impact of HCQ over a consecutive 10-year period on the risk of DM in an SLE population.
Results: Following propensity matching an equal cohort, 19025 SLE patients on HCQ and 19025 SLE controls, were included with a mean period of follow-up of 10 years. Patients who were adherent to HCQ had lower rates of DM (event rate: 13.3% vs 18.5%) with relative risk (RR) 72.0% (68.7% to 75.4%). In Kaplan-Meier survival analysis the cumulative probability of survival was significantly higher in the HCQ subjects compared to control (78.1% vs 68.3%; log-rank, $p<0.001$).
Conclusion: We provide further evidence for the antidiabetic effect of hydroxychloroquine in a lupus cohort. We suggest a unifying hypothesis linking the pharmacologic effect of hydroxychloroquine with its favorable effects on glucose metabolism.

Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with protean manifestations affecting most organ systems. Antimalarial including hydroxychloroquine (HCQ) and chloroquine have been a cornerstone of SLE management with proven efficacy on survival, reducing the burden of disease including flares, and reducing the risk of irreversible organ damage, venous thromboembolism, and hyperlipidemia [1]. In an age stratified observational study of the impact of cardiovascular risk factors in predicting coronary artery disease (CAD) in patients with SLE, we noted that the prevalence of type II diabetes mellitus (DM) was significantly less in SLE than in control populations [2]. Additionally, these results were observed in 3 separate age groups studied (age 18−35, 36−55, and > 55 years). The metabolic effect was most apparent in the age group 18−35 years. We speculated that HCQ, an FDA approved treatment for SLE, could be a contributing factor to the protective metabolic effect as suggested by a number of authors [3−5]. To further explore the epidemiologic impact of HCQ on the risk for DM we employed a browser based real time analytic platform, TriNetX and a propensity score matching (PSM) approach.

Patients and methods

Data source

TriNetX is a global federated health research network that provides real-world anonymized electronic medical records data including diagnosis, procedures, medications, laboratory values, and genomic information of patients in 55 healthcare organizations

Abbreviations: DM, Diabetes Mellitus; HCQ, Hydroxychloroquine; SLE, Systemic Lupus Erythematosus

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https://doi.org/10.1016/j.deman.2022.100089

Table 1
Baseline characteristics of study population before and after propensity score matching.

	Before propensity score Matching			After propensity score Matching		
Characteristic Name	HCQ[1] n=25612	No HCQ n=38522	[2]SMD	HCQ n=19025	No HCQ n=19025	SMD
Age at Index	47 (15)	52 (15)	0.32	50 (15)	50 (15)	0.05
Female	90.9%	87.3%	0.12	89.9%	90.2%	0.01
White	52.7%	62.4%	0.2	56.3%	58.5%	0.04
Black or African American	29.6%	22.9%	0.15	27.5%	26.3%	0.03
Male	9.1%	12.7%	0.12	10.1%	9.8%	0.01
Asian	2.4%	1.7%	0.05	2.2%	1.9%	0.02
hydroxychloroquine	100.0%	0.0%		100.0%	0.0%	
Glucocorticoids	85.7%	57.1%	0.67	80.9%	82.4%	0.04
Antilipemic Agents	26.6%	27.7%	0.03	28.4%	29.8%	0.03
ACE[3] Inhibitors	27.3%	18.6%	0.21	24.5%	24.0%	0.01
methotrexate	19.7%	5.5%	0.44	10.5%	10.3%	0
azathioprine	16.9%	4.2%	0.42	8.0%	8.0%	0
cyclosporine	6.3%	2.8%	0.17	4.7%	4.5%	0.01
rituximab	4.2%	1.6%	0.16	2.7%	2.6%	0.01
leflunomide	4.3%	1.3%	0.18	2.5%	2.3%	0.01
belimumab	5.5%	0.7%	0.28	1.6%	1.4%	0.01
mycophenolate	1.8%	0.3%	0.14	0.7%	0.6%	0.01
Essential (primary) hypertension	45.0%	52.2%	0.14	47.7%	46.9%	0.02
Lipid disorders	26.6%	37.3%	0.23	30.4%	30.7%	0.01
Mood [affective] disorders	28.7%	30.0%	0.03	29.4%	29.1%	0.01
Disorders of thyroid gland	27.1%	29.3%	0.05	27.5%	30.5%	0.07
Overweight and obesity	23.5%	27.5%	0.09	25.3%	25.2%	0
Diabetes mellitus	22.0%	23.0%	0.02	22.6%	22.4%	0.01

[1] ACE (Angiotensin converting enzyme)
[2] HCQ: Hydroxychloroquine, 3SMD: Standardized mean difference.

(HCO) including private and academic medical centers, and primary care and specialist providers across the United States [6]. Quality assurance is achieved at the time of data extraction in a standardized format from EHRs before inclusion in the federated network database. A total of 74 million patient records are included in TriNetX HCOs. TriNetX is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Since data are de-identified, no IRB approval is required.

Study population and end points

The research database was queried for all patients aged ≥18 years diagnosed with SLE from January 1, 2000, until January 1, 2021. We identified patients with SLE using disease−specific International Classification of Diseases, Tenth Revision, ICD-10-CM Code: M32. At the time of enrollment, we excluded all patients who were diagnosed with DM, ICD-10-CM Code: E08-E13 either prior to or at the initial visit. Patients were classified into two groups according to treatment status with HCQ. We defined the treatment group as patients who were adherent to HCQ as documented in consecutive annual visits for 3 years prior to trial initiation according to concomitant medication lists noted at each visit. The control group consisted of SLE patients also seen at consecutive annual visits over 3 years who were not receiving HCQ documented in the medication lists. The primary objective was to compare the impact of HCQ over a consecutive 10-year period on the risk of DM in an SLE population. Baseline demographic data, comorbidities and medication usage were captured from the patient EMR in which only aggregate data and statistical summaries are provided.

Statistical analysis

Statistical analysis was conducted utilizing the TriNetX platform in real time. Categorical variables are reported as percentages. Continuous variables are reported as the mean (±) standard deviation (SD). Patient demographic data, medication usage and comorbidities were compared between groups using standardized mean difference (SMD). Effect size is considered large, moderate, small and trivial for values > 0.5, 0.3−0.4, 0.1−0.2 and < 0.1 respectively [7]. We generated two matched cohorts, one with and one without treatment with HCQ, using a PSM nearest-neighbor (1:1) matching algorithm with a caliper of 0.1 pooled SDs (Supp. Figure 1). Variables included in the PSM models were age, sex, race, and cardiovascular risk factors including hypertension, hyperlipidemia, and obesity. In addition to medications for cardiometabolic diseases, we included medications used in the treatment of SLE including steroids and immunomodulating medications (Table 1). We compared the incidence and relative risk (RR) of DM in matched study cohorts. We estimated the cumulative incidence curves of DM in patients treated with HCQ using the Kaplan-Meier (K-M) method. We assessed the statistical significance of the difference in censored data between the two groups using the log−rank test

Sensitivity analysis

Subgroup analysis was performed based on the age of the patient at the time of enrollment. Age groups were divided into young (18 −35 years), middle (36−55 years) and above 55 years of age. A PSM cohort with and without HCQ treatment was developed in each age group. The relative risk and cumulative incidence curves for DM were calculated.

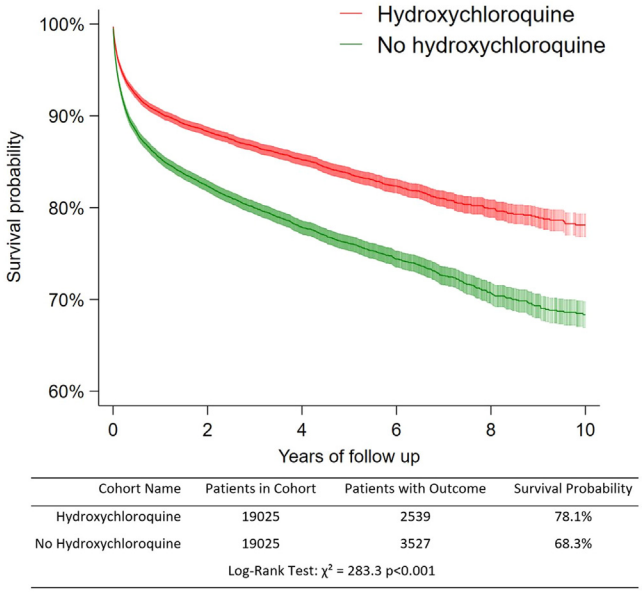
Results

We studied a total population of 25,612 SLE patients on HCQ and 38,522 SLE controls with a mean period of follow-up of 10 years. Table 1 summarizes the demographic and clinical characteristics of the study populations. In both groups, women predominate. In the HCQ population, the average age was younger with mean age ± SD (47 (±15) vs 52 (±15) years, SMD=0.3), and the proportion of White patients was lower (52.7% vs 62.4%, SMD=0.2). The percentage of concomitant medications with immunomodulatory properties used in SLE patients treated with HCQ was significantly different than in the control group; glucocorticoid, 85.7% on HCQ vs 57.1% in controls, (SMD=0.7); methotrexate, 19.7% on HCQ vs 5.5% in controls, (SMD=0.4); and azathioprine, 16.9% on HCQ vs 4.2% in controls, (SMD=0.4). Furthermore, the HCQ group had a lower prevalence of hypertension and lipid disorders.

Table 2
Risk for diabetes mellitus in patients with and without use of hydroxychloroquine in propensity score matched group following 10 years follow up.

Cohort Name	HCQ Pts with Outcome	Non HCQ Pts with Outcome	Risk Difference and 95% CI	Risk Ratio and 95% CI
Total (n=19025)	2539 (13.3%)	3527 (18.5%)	-5.2% (-5.9% to -4.5%) $p<0.00$	72.0% (68.7% to 75.4%)
Young (n=5604)	416 (7.4%)	600 (10.7%)	-3.3% (-4.3% to -2.2%) $p<0.00$	69.3% (61.5% to 78.1%)
Middle age (n=11721)	1610 (13.7%)	2285 (19.5%)	-5.8% (-6.7% to -4.8%) $p<0.00$	70.5% (66.5% to 74.7%)
Old age (n=9029)	1639 (18.2%)	2218 (24.6%)	-6.4% (-7.6% to -5.2%) $p<0.00$	73.9% (69.8% to 78.2%)
Steroid users (n=7654)	1384 (18.1%)	1918 (25.1%)	-7.0% (-8.3% to -5.7%) $p<0.00$	72.2% (67.9% to 76.7%)

HCQ: Hydroxychloroquine



Cohort Name	Patients in Cohort	Patients with Outcome	Survival Probability
Hydroxychloroquine	19025	2539	78.1%
No Hydroxychloroquine	19025	3527	68.3%

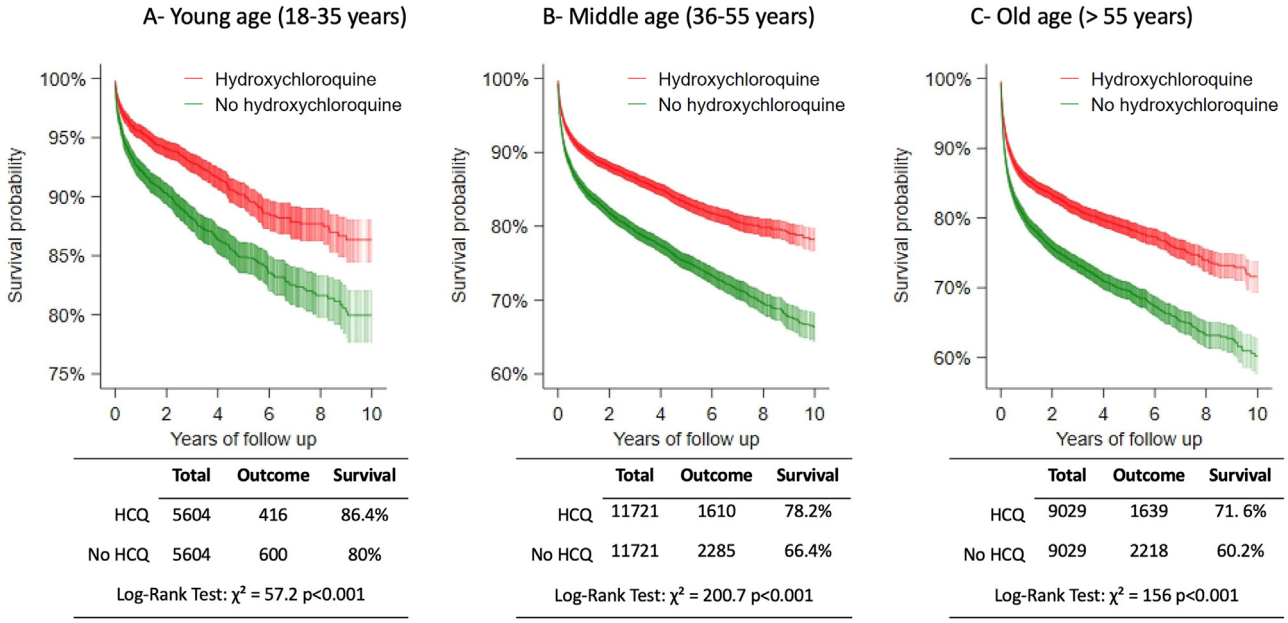
Log-Rank Test: $\chi^2 = 283.3$ p<0.001

Fig. 1. Kaplan-Meier estimates for the incidence of diabetes mellitus in SLE patients with hydroxychloroquine (red) and no hydroxychloroquine (green) after propensity score matching. (Shaded areas are 95% Cis).

To reduce bias due to confounding, PSM was employed. Patients who were adherent to HCQ throughout the ten-year follow-up period as determined by TriNetX data had lower rates of DM (event rate: 13.3% vs 18.5%) with risk difference of -5.2% (-5.9% to -4.5%) $p<0.001$ and RR 72.0% (68.7% to 75.4%) (Table 2). In K-M survival analysis the cumulative probability of survival free of DM, was significantly higher in the HCQ subjects compared to control (78.1% vs 68.3%: log-rank, $p<0.001$) (Fig. 1). From the survival curve, as the duration of HCQ treatment is extended from baseline through 10 years, the probability of survival free of DM decreases equally in both HCQ and control groups. The robustness of the data was assessed through evaluating RR (shown in Table 2), and K-M survival in various age groups. As expected, the risk of DM increased with age. In young patients age, 18–35 years, the event rate was 7.4% in patient on HCQ vs 10.7% in controls which increased to 18.2% in patients on HCQ vs 24.6% in control patients over 55 years. In all three age groups the cumulative survival for DM was significantly better in patients on HCQ (Fig. 2).

Discussion

Using a large cohort of subjects captured in the TriNetX real-world database, and PSM scoring, we have demonstrated that HCQ reduces the risk of DM among SLE patients. The reduced risk of DM is sustained over the ten-year period of observation, independent of cardiometabolic risk factors including treatment for hypertension and



	Total	Outcome	Survival
HCQ	5604	416	86.4%
No HCQ	5604	600	80%

Log-Rank Test: $\chi^2 = 57.2$ p<0.001

	Total	Outcome	Survival
HCQ	11721	1610	78.2%
No HCQ	11721	2285	66.4%

Log-Rank Test: $\chi^2 = 200.7$ p<0.001

	Total	Outcome	Survival
HCQ	9029	1639	71. 6%
No HCQ	9029	2218	60.2%

Log-Rank Test: $\chi^2 = 156$ p<0.001

Fig. 2. Kaplan-Meier estimates for the incidence of diabetes mellitus in different age groups of SLE patients with hydroxychloroquine (red) and no hydroxychloroquine (green) after propensity score matching.(Shaded areas are 95% Cis).

hyperlipidemia, as well as independent of glucocorticoids and other immunomodulatory drugs used in the management of SLE. Notably, this sustained effect is consistent in the three age groups studied, though the best survival experience is seen in the youngest age group, 18-35 year (Fig. 2). With age, the mitigating effect of HCQ on DM, though still present, diminishes consistent with the overall age-related increase in the incidence of DM.

The present results are consistent with our earlier observation in which the impact of DM in CAD was least in young age groups and increased with age in an analysis of risk factors contributing to CAD in SLE [2]. HCQ had little or no effect on CAD risk factors other than DM and HbA1C. In the present study, comorbidities that we evaluated did not impact the protective effect of HCQ. Furthermore, in patients on glucocorticoids or immunomodulating treatment, HCQ was still effective in decreasing the incidence of DM. While we did not specifically address the effect of HCQ on other risk factors such as hyperlipidemia or hypertension, we did note a lipid lowering effect as well as improved blood pressure in the treated cohort prior to adjustment for confounding. Petri et al showed a cholesterol lowering effect of HCQ in the Hopkins Lupus cohort [8]. Chen et al showed that the risk of DM increased with high dose glucocorticoids [3]. Risk decreased with concomitant HCQ use. They also observed that a reduced hazard ratio of DM was associated with a cumulative HCQ dosage $\geq$ 129g. While we do not have information on medication dosage, at usual dosage of HCQ in the treatment of SLE (400mg daily), the cumulative dosage at three years would greatly exceed 129g. Shahrzad et al emphasized the importance of compliance of antimalarials to sustain the anti-DM benefits of therapy [4].

Molecular mechanisms employed by HCQ in the treatment of SLE and other autoimmune syndromes are complex and not fully understood. Both inflammatory and metabolic pathways are altered [9]. Using Bioinformatic and Poly-pharmacology tools Xie et al suggest that HCQ inhibits activation and proliferation of T cells, and down regulates both type 1 IFN and cytokine production [10]. Antidiabetogenic effects of HCQ include improved beta cell function and insulin sensitivity in non-diabetic as well as diabetic individuals [11,12]. A novel finding in the trial by Wasko et al was improved adiponectin levels which they suggest may mediate the favorable effects on glucose metabolism [13]. In a pre-clinical study rats fed a diet high in free fatty acids, lipotoxicity and hyperglycemia due to infiltration of mononuclear cells and a chronic inflammatory state of the pancreas was prevented by concomitant HCQ [14]. A possible link between the metabolic and anti-inflammatory effect of HCQ is adiponectin, an adipocyte specific protein in which deficiency is associated with insulin resistance, obesity and type 2 diabetes [15]. Adiposity is a negative predictor of adiponectin [16]. A transcriptional factor which augments adiponectin is peroxisome proliferator-activated receptor (PPAR) gamma whose conformational structure is influenced by synthetic agonist such as thiazolidinediones (TZD) medications [17]. The effect is both a decrease in inflammatory cytokines and increased adiponectin thus providing a functional link between the two mechanisms. While temporal association may not imply causation, an agonist effect of HCQ on a PPAR pathway could result in improved metabolic function. Further pharmacologic data will be required to resolve this question.

Limitations

Observational data with large sample size present several limitations. Accuracy of EMR records cannot be verified with errors possible in ICD coding. Residual confounding is always possible even when informed adjustments are considered. For example, socioeconomic status, and different healthcare settings may not be accounted for. Medication adherence and dosage is also not available in the TriNetX files. Lastly, due to the large sample size of the database, the present results may not be generalized to restricted segments of the population. A large sample size can also exaggerate small clinical differences.

Conclusion

In summary, using a database covering a wide segment of the SLE population, we provide further evidence for the antidiabetic effect of hydroxychloroquine in a lupus cohort over a ten-year period. The effect is sustained and consistent across all adult age groups studied. Furthermore, the effect is independent of cardiovascular risk factors and treatment, as well as immunomodulatory medications used in the treatment of SLE. Lastly, we suggest a unifying hypothesis linking the pharmacologic effect of hydroxychloroquine with its favorable effects on glucose metabolism .

Declaration of conflict of interest

This manuscript constitutes original research that has not been published nor submitted to any other journal for consideration.

All authors contributed to the manuscript and have approved it for submission.

None of the authors have any conflicts of interest to declare.

Acknowledgement

The TriNetX data and analytics tool set is available at the Medical College of Wisconsin and the Clinic and Translational Science Institute of Southeast Wisconsin and is funded by NCATS Clinical and a Translational Science Award grant, 5UL1TR001436.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.deman.2022.100089.

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