Hydroxychloroquine and Risk of Diabetes in Patients With Rheumatoid Arthritis

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TYPE 2 DIABETES MELLITUS AFFECTS nearly 8% of US adults, and its prevalence has been increasing.1,2 Diabetes is a major cause of morbidity and mortality, with costly sequelae that include atherosclerotic disease, renal failure, and blindness. Given the importance of diabetes as a national health problem, efforts to identify treatments that can prevent this disorder have gained priority. Recent studies suggest that lifestyle modifications and medications such as ramipril, rosiglitazone, and metformin can postpone the development of diabetes mellitus.3-7

Antimalarials such as hydroxychloroquine, a long-standing safe and inexpensive treatment for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, theoretically may improve glucose tolerance and prevent diabetes mellitus. In vitro and animal studies indicate that antimalarials improve insulin secretion and peripheral insulin sensitivity.8-11 Hypoglycemia is a rare but well recognized adverse effect of treatment with antimalarials.12 Antimalarials also have been shown to lower glycated hemoglobin levels in patients with type 2 diabetes who have suboptimal glucose control.13 In addition, the prevalence of diabetes in patients with rheumatoid arthritis is similar to that of other patients, even though patients with rheumatoid arthritis are more sedentary and often treated with corticosteroids that induce weight gain.14,15

This study was designed to investigate the association between hydroxychloroquine therapy and risk of incident diabetes in patients with rheumatoid arthritis. We hypothesized that hydroxychloroquine use would be associated with a decreased likelihood of the development of diabetes. This study examines the incidence of diabetes by hydroxychloroquine exposure status in an established rheumatoid arthritis cohort with prospective follow-up for more than 20 years.

Context Hydroxychloroquine, a commonly used antirheumatic medication, has hypoglycemic effects and may reduce the risk of diabetes mellitus.

Objective To determine the association between hydroxychloroquine use and the incidence of self-reported diabetes in a cohort of patients with rheumatoid arthritis.

Design, Setting, and Patients A prospective, multicenter observational study of 4905 adults with rheumatoid arthritis (1808 had taken hydroxychloroquine and 3097 had never taken hydroxychloroquine) and no diagnosis or treatment for diabetes in outpatient university-based and community-based rheumatology practices with 21.5 years of follow-up (January 1983 through July 2004).

Main Outcome Measures Diabetes by self-report of diagnosis or hypoglycemic medication use.

Results During the observation period, incident diabetes was reported by 54 patients who had taken hydroxychloroquine and by 171 patients who had never taken hydroxychloroquine, with incidence rates of 5.2 per 1000 patient-years of observation compared with 8.9 per 1000 patient-years of observation, respectively (P < .001). In time-varying multivariable analysis with adjustments for possible confounding factors, the hazard ratio for incident diabetes among patients who had taken hydroxychloroquine was 0.62 (95% confidence interval, 0.42-0.92) compared with those who had not taken hydroxychloroquine. In Poisson regression, the risk of incident diabetes was significantly reduced with increased duration of hydroxychloroquine use (P < .001 for trend); among those taking hydroxychloroquine for more than 4 years (n = 384), the adjusted relative risk of developing diabetes was 0.23 (95% confidence interval, 0.11-0.50; P < .001), compared with those who had not taken hydroxychloroquine.

Conclusion Among patients with rheumatoid arthritis, use of hydroxychloroquine is associated with a reduced risk of diabetes.

METHODS Participants Men and women with a diagnosis of rheumatoid arthritis established at age 16 years or older were eligible for enrollment in the Arthritis, Rheumatism, and Aging Medical Information Sys-

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HYDROXYCHLOROQUINE AND RISK OF DIABETES

At each phase, participants reported known risk factors for diabetes and other characteristics of interest, including comorbid conditions (prevalent and incident), height, weight, medication use, and functional status summarized in the HAQ disability index (HAQ-DI). The well-validated HAQ-DI is based on responses to 20 questions about degree of difficulty (none = 0, some difficulty = 1, much difficulty = 2, and unable to do = 3) in completing activities within 8 functional categories (dressing/grooming, arising, eating, walking, personal hygiene, reaching, gripping, and doing errands and chores). The HAQ-DI score, ranging from 0 to 3 units, is an average of the scores for these 8 domains, with a score of 0 reflecting no disability and a score of 3 indicating severe disability. \(^*\)

Body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was determined for each phase along with a maximum value. Duration of rheumatoid arthritis was ascertained at study entry. Use of hydroxychloroquine, prednisone, and methotrexate was evaluated as ever or never use, and the percentage of time taking the drug during the observation period was calculated as the number of phases taking the drug divided by the total number of phases under observation. Demographic characteristics, including age at entry, sex, race (by self-report), years of education, and practice site also were examined in conjunction with diabetes risk. Because standard rheumatoid arthritis drug therapies as well as the thresholds for diabetes diagnosis have evolved over time, year of study entry was included as a variable of interest.

### Outcome

The primary outcome was incident diabetes mellitus defined by newly reported disease or new use of hypoglycemic medication(s). Diagnosis date for diabetes was assigned at the HAQ phase (6-month) midpoint. To verify newly reported diabetes without pharmacological treatment, use of hypoglycemic medications reported in subsequent phases was determined to confirm diagnosis.

### Statistical Analysis

Patients with rheumatoid arthritis without diabetes were classified according to ever or never use of hydroxychloroquine during the observation period. Characteristics of the 2 groups were compared using \(\chi^2\) tests for categorical data and \(t\) tests for continuous variables. A Kaplan-Meier survival curve demonstrating probability of developing diabetes was constructed according to hydroxychloroquine exposure status (ever or never use). Additional Kaplan-Meier curves for diabetes were generated by duration of hydroxychloroquine use and compared with those with never use over the same periods. This approach allowed for comparison of diabetes risk by exposure, adjusting for different observation time among the groups.

To examine the risk (or hazard) of developing diabetes (adjusted for the possible confounding effects of other factors on the outcome), multivariable regression models were constructed in 2 ways. First, time-varying Cox proportional hazards regression models were examined using all of the 6-month follow-up data, thus allowing medication use and covariates to change over time. This approach also accounted for changes in standard drug therapy for rheumatoid arthritis as well as variations in the threshold for diagnosing and treating diabetes during the observation period. For example, in the Cox time-varying regression, if individuals were not taking hydroxychloroquine during certain phases of the study (possibly at study entry or if they stopped taking hydroxychloroquine before censoring or the end of the observation period), they would contribute to the estimates for patients in the never use category during those periods. Thus, the time-varying model takes all observations until censoring or dropout into account, even if a participant was not taking hydroxychloroquine at study entry or if a person stopped taking hydroxychloroquine later on.

To assess cumulative dose-related effects of hydroxychloroquine, an ordered categorical variable was established based on approximate quartiles.
of duration of use in the patients taking hydroxychloroquine. A Poisson regression model was then constructed to test the relationship between duration of drug exposure and risk of incident diabetes, providing adjusted relative risks for each category of hydroxychloroquine use compared with patients with never use. In contrast to the time-varying regression model, the observation time in the Poisson analysis for patients with hydroxychloroquine ever use began at initiation of hydroxychloroquine. Incident diabetes rates were calculated for each of the 4 groups for duration of hydroxychloroquine use and compared with patients with never use.

Results of the Poisson analysis examining duration of hydroxychloroquine use were verified using a standard Cox proportional hazards model using the same covariates and observation times.20

In both the Cox time-varying and Poisson models, potential confounding factors were addressed by adjustment and included use of prednisone and methotrexate (yes or no or percentage age time taking drug for the Poisson model), BMI, age, sex, education, race, year of entry, rheumatoid arthritis duration at entry, and HAQ-DI. Because data were collected in multiple centers, a study site was used for stratification in all multivariable analyses to account for unmeasured site-related variations that may have affected outcomes.

Interactions between potentially related variables (hydroxychloroquine and prednisone, prednisone and methotrexate, hydroxychloroquine and methotrexate, prednisone and HAQ-DI, prednisone and BMI, and BMI and HAQ-DI) also were tested in the Cox time-varying model. For both regression analyses, missing values of independent variables were replaced with group means.

Statistical analyses were conducted using SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Prevalent cases of diabetes (n = 211) who were excluded from the analysis were more likely than the included patients to be male, older at entry, nonwhite, less educated, have a higher entry HAQ-DI score, and higher maximum BMI during the observation period (P < .001 for each). Most of these factors also were associated with diabetes incidence in the follow-up study. The 627 patients excluded due to lack of longitudinal data (ie, who completed only 1 HAQ) also were more likely to be male, nonwhite, less educated (P < .001 for each), to have a higher entry HAQ-DI score (P < .01), and a lower maximum BMI (P < .05).

Of the remaining 4905 patients included in the study, 1808 (37%) reported hydroxychloroquine use at some time during the observation period. Average HAQ response rates were 89% for never users and 91% for ever users.

Patterns of Hydroxychloroquine Use

On average, hydroxychloroquine dosing was 340 mg/d over the course of follow-up; 64% of patients took 400 mg/d. Of the 1808 patients with hydroxychloroquine ever use, 1035 (57%) were taking hydroxychloroquine at study entry. The remaining 773 patients (43%) in the ever-use group started taking hydroxychloroquine during the observation period (ie, after study entry). On average, patients with hydroxychloroquine ever use were taking the drug 55% of the observation time. Discontinuation of hydroxychloroquine for at least 1 year before censoring or the end of the observation period occurred in 32% of all patients with ever use. Hydroxychloroquine was taken for an average of 3.1 years; median hydroxy-

Table 1. Characteristics of Patients With Rheumatoid Arthritis by Hydroxychloroquine Use

<table>
<thead>
<tr>
<th>Hydroxychloroquine Use</th>
<th>Never (n = 3097)</th>
<th>Ever (n = 1808)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>744 (25)</td>
<td>354 (19.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>White race</td>
<td>2778 (89.7)</td>
<td>1613 (89.2)</td>
<td>.59</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>1797 (58)</td>
<td>1298 (72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1520 (49)</td>
<td>1155 (64)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, y</td>
<td>12.6 (2.8)</td>
<td>13.3 (2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age, y</td>
<td>58.2 (13.9)</td>
<td>53.7 (14.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of rheumatoid arthritis, y</td>
<td>13.0 (11.7)</td>
<td>8.4 (9.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HAQ-DI score</td>
<td>1.7 (0.8)</td>
<td>1.1 (0.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Maximum BMI during observation period</td>
<td>27.7 (5.8)</td>
<td>28.0 (6.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Duration of medication use, % of observation time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>36 (40)</td>
<td>41 (38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>32 (39)</td>
<td>37 (37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>55 (35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: HAQ-DI, Health Assessment Questionnaire disability index.

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Incidence of diabetes was 3.1 years (range, 0.5-21.5 years). Of the 54 patients with hydroxychloroquine ever use diagnosed with diabetes, 30 were taking the drug at the time of diagnosis.

**Incident Diabetes Rates and Hydroxychloroquine Ever Use vs Never Use**

Incident diagnoses of diabetes were reported by 54 patients with ever use of hydroxychloroquine and 171 patients with never use (Table 2). Of those patients reporting a new diagnosis of diabetes but not taking hypoglycemic medication, 70% of patients with never use of hydroxychloroquine and 48% of patients with hydroxychloroquine ever use reported use of diabetes drug(s) during subsequent follow-up.

On average, patients with hydroxychloroquine ever use were observed for 5.7 years until developing diabetes or censoring by drop-out, study conclusion, or death compared with 6.2 years for patients with never use. Patients with hydroxychloroquine ever use developed diabetes after 4.8 years of observation on average compared with 4.2 years in the patients with never use; this difference was not statistically significant (P = .35). Incidence rates for diabetes were 8.9 per 1000 patient-years of observation for patients with never use vs 5.2 per 1000 patient-years of observation for patients with hydroxychloroquine ever use (P < .001). Diabetes incidence rates also varied significantly across centers (P = .006).

The difference in probability of developing diabetes in those with hydroxychloroquine ever use compared with those with never use was statistically significant over time (P > .001), with those with hydroxychloroquine ever use being less likely to develop diabetes throughout the 21.5-year follow-up period (Figure).

**Hydroxychloroquine Use and Diabetes Risk**

Results of the Cox time-varying multivariable regression showed a significant reduction in risk of diabetes for patients with hydroxychloroquine use compared with those with never use at each phase (Table 3). This finding persisted with the addition to the models of demographic characteristics, known risk factors for diabetes, and rheumatoid arthritis–related covariates (hazard ratio, 0.62; 95% confidence interval [CI], 0.42-0.92). None of the interaction terms considered, including all interactions between hydroxychloroquine, methotrexate, and prednisone, were significantly associated with the outcome and did not alter the observed results regarding hydroxychloroquine use.

**Hydroxychloroquine Duration and Diabetes Risk**

In Poisson regression with adjustment for possible confounding factors, the relative risk of developing diabetes progressively declined with increasing time taking hydroxychloroquine (P < .001 for trend; Table 4). Patients who took hydroxychloroquine for more than 4 years had a significantly lower risk of diabetes compared with those who had never taken hydroxychloroquine (relative risk, 0.23; 95% CI, 0.11-0.50). In a Cox proportional hazards analysis as a comparison, the strength of the association of reduced risk of diabetes also increased with duration of hydroxychloroquine exposure; in those taking hydroxychloroquine for more than 4 years (n = 384), the hazard ratio for developing diabetes was 0.22 (95% CI, 0.10-0.48; P < .001).

The observation time in patients with never use was similar to the observation time in all duration categories of hydroxychloroquine use, except for more than 4 years of use, in which the observation time was longer on average. Thus, it is possible that the effect observed in the Poisson regression for the longest duration of hydroxychloroquine use was an artifact of this difference. To address this issue, Kaplan-Meier curves based on duration of hydroxychloroquine use were compared with patients with never use over the same observation times. Results comparing curves in patients with hydroxychloroquine use with those with never use showed a progressive reduction in incident diabetes risk with greater duration of hydroxychloroquine use (≤1 year, P = .52; >1 to 2 years, P = .29; >2 to 4 years, P = .08; and >4 years, P < .001). The comparison of patients who took hydroxychloroquine for more than 4 years with those with never use showed significantly lower probability of diabetes over time in those using hydroxychloroquine more than 4 years (Figure). Risk reduction among those with hydroxychloroquine use for more than 4 years ranged from 0.06 to 0.47 at specific time points during the observation period.

**COMMENT**

We report herein the first evidence, to our knowledge, suggesting that use of hydroxychloroquine is associated with a reduced risk of developing diabetes in patients with rheumatoid arthritis. This reduction in diabetes risk persisted after adjusting for diabetes risk factors and other covariates such as BMI, functional status, and corticosteroid use. Moreover, risk reduction increased with duration of hydroxychloroquine exposure, supporting a biological action of this drug on glucose metabolism. These results show a reduction in diabetes risk of up to 77% for patients taking hydroxychloroquine for more than 4 years, a finding that is comparable or superior to that of other drugs studied in clinical trials.
rosiglitazone, combination hormone therapy, estrogen only, metformin, acarbose, and ramipril.

Antimalarial agents have been reported to cause both symptomatic and asymptomatic hypoglycemia. Antimalarial agents also have been explored as an adjunct to insulin and oral hypoglycemic agents for poorly controlled type 2 diabetes. Patients with non–insulin-dependent diabetes with suboptimal disease control during an intensive outpatient intervention showed an absolute reduction in glycated hemoglobin $A_1C$ level of 3.3% when treated for 6 months with hydroxychloroquine dosed at 200 mg 3 times per day. In a trial of patients with type 2 diabetes who had poor glycemic control despite taking maximal doses of sulfonylureas, the addition of hydroxychloroquine improved glycemic control, with greatest benefit in those with baseline hemoglobin $A_1C$ levels lower than 13.5%. Petri reported a significantly lower mean glucose level among participants in the Baltimore Lupus Cohort while they were taking hydroxychloroquine, as well as a protective effect of hydroxychloroquine on abnormal glucose tolerance testing.

The present study reports 2 unique findings. First, hydroxychloroquine use was associated with reduction in risk of incident diabetes. This result is not surprising based on the changes in glucose metabolism described in patients with type 2 diabetes and in patients with lupus. Moreover, this association with reduced risk of diabetes was related to duration of hydroxychloroquine exposure. Second, those who had taken hydroxychloroquine compared with those who had never taken the drug who had prevalent disease or developed diabetes during the follow-up observation period were less likely to report use of hypoglycemic medication. Hydroxychloroquine use may modify the clinical manifestations of hyperglycemia, or it may attenuate hyperglycemia and reduce the need for hypoglycemic medications once this diagnosis is established.

Based on the age of the participants in our study and the rates of diabetes medication use after self-reported diabetes diagnosis, we speculate that the majority of patients with incident diabetes most likely have type 2 diabetes mellitus. However, the anti-inflammatory effects of rheumatoid arthritis medications may at-

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**Figure.** Probability of Developing Diabetes in Rheumatoid Arthritis Patients According to Hydroxychloroquine Use

<table>
<thead>
<tr>
<th>Observation Period, y</th>
<th>Probability of Developing Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>1-2</td>
<td>0.04</td>
</tr>
<tr>
<td>&gt;2-4</td>
<td>0.06</td>
</tr>
<tr>
<td>&gt;4</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*P* <.001 for comparison between the groups.

**Table 3.** Risk of Developing Diabetes in Patients With Rheumatoid Arthritis*

<table>
<thead>
<tr>
<th>Hydroxychloroquine Use</th>
<th>Adjusted for Sex, Age, and Year of Study Entry</th>
<th>Additionally Adjusted for Race and Education</th>
<th>Additionally Adjusted for Rheumatoid Arthritis Duration at Entry, HAQ-DI, BMI, and Methotrexate and Prednisone Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (95% CI)</td>
<td>Adjusted for Sex, Age, and Year of Study Entry</td>
<td>Additionally Adjusted for Race and Education</td>
<td>Additionally Adjusted for Rheumatoid Arthritis Duration at Entry, HAQ-DI, BMI, and Methotrexate and Prednisone Use</td>
</tr>
<tr>
<td>Never Use</td>
<td>0.60 (0.40-0.89)</td>
<td>0.62 (0.42-0.92)</td>
<td>0.62 (0.42-0.92)</td>
</tr>
<tr>
<td>Ever 1-2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4.** Risk of Developing Diabetes in Patients With Rheumatoid Arthritis by Duration of Hydroxychloroquine Use

<table>
<thead>
<tr>
<th>Duration of Hydroxychloroquine Use, y</th>
<th>No. of patients</th>
<th>Adjusted RR (95% CI)*</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never Use</td>
<td>3097</td>
<td>0.83 (0.51-1.34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1-2</td>
<td>532</td>
<td>0.71 (0.39-1.29)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>&gt;2-4</td>
<td>306</td>
<td>0.65 (0.38-1.10)</td>
<td>.03</td>
</tr>
<tr>
<td>&gt;4</td>
<td>376</td>
<td>0.23 (0.11-0.50)</td>
<td>.01</td>
</tr>
</tbody>
</table>

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tenuate both type 1 and type 2 diabetes onset, given the autoimmune nature of type 1 diabetes and the role of chronic inflammation in insulin resistance that characterizes type 2 diabetes. In addition, because those with hydroxychloroquine use also were more likely to be taking methotrexate and prednisone, they probably were more likely to have regular encounters with medical professionals and have more frequent laboratory testing, whereby asymptomatic hyperglycemia might be detected.

Substantial differences were noted in the characteristics of the rheumatoid arthritis groups that reported ever use of hydroxychloroquine vs never use during the observation period. Those with never use of hydroxychloroquine were older, had longer rheumatoid arthritis disease duration, were more disabled as indicated by their HAQ scores, and thus may have been considered less viable candidates for immunosuppressive therapy than those with hydroxychloroquine ever use, as suggested by the lower rates of use of prednisone and methotrexate in this group.

Differences between groups in year of study entry are consistent with these findings because those with never use were observed earlier when less aggressive treatment strategies were used, and fewer treatment options were available. Such factors may have resulted in less frequent “routine” encounters with health care professionals and less frequent laboratory testing. A higher likelihood of being diagnosed with diabetes or receiving hypoglycemic therapy would be expected with closer health care surveillance, which occurs during monitoring for medication toxic effects and dose adjustments. Although such ascertainment bias could have resulted in higher rates of diabetes in those with hydroxychloroquine ever use, this supposition was not supported by the data. Differences in medical surveillance could have resulted in underestimation of diabetes rates in those with never use and risk reduction in the hydroxychloroquine ever use group. Despite the differences between the 2 study groups, the overall characteristics of this study cohort reflect those of a typical outpatient practice of patients with rheumatoid arthritis in North America.

We used a time-varying regression model to assess hydroxychloroquine effects on risk of incident diabetes not only because standard rheumatoid arthritis treatment has evolved over time but also because the threshold for rendering a diagnosis of diabetes has been modified. Use of the time-varying model enabled us to adjust for variations in these factors and for changes in possible confounders at each 6-month interval over the 21.5 years of observation, and allowed a more accurate reflection of total rheumatoid arthritis treatment over time.

Antimalarials have been an appealing treatment option in rheumatic diseases because decades of experience in taking these drugs provided a breadth of knowledge about their potential adverse effects. While the disease-modifying properties are not as dramatic as other current treatment options for rheumatoid arthritis, the toxicity profile of hydroxychloroquine is superior to other traditional disease-modifying antirheumatic drugs and biological therapies, leading to its use in mild to moderate disease and in combination therapy for rheumatoid arthritis. Unlike these other agents, the antimalarials confer no increased risk of infection or malignancy, and the risk of adverse effects on internal organs is minimal when dosed according to body weight. Furthermore, the drug is well tolerated, and toxicity laboratory monitoring is not routinely indicated. While retinal toxicity is rare, most physicians recommend yearly or semi-annual ophthalmologic examinations.

The mechanisms of hypoglycemia with hydroxychloroquine are inferred from studies of chloroquine, a structurally similar antimalarial with similar indications but less widespread use due to a greater risk of retinal toxicity. Chloroquine has been shown to alter insulin metabolism in humans by both increasing insulin secretion and inhibiting its clearance, leading to hypoglycemia. Animal data have shown increased insulin levels in hydroxychloroquine-treated diabetic rats. Hydroxychloroquine also has been shown to inhibit insulin metabolism in rat liver cells.

While our study showed a reduction in diabetes incidence specifically in a rheumatoid arthritis cohort taking hydroxychloroquine, these findings also may be expected to occur in patients without rheumatoid arthritis. The beneficial changes in glucose metabolism and insulin sensitivity reported among patients with lupus, patients with type 2 diabetes, and in animal models suggest that these effects are not specific to rheumatoid arthritis. The fact that antimalarials favorably affect dyslipidemia in patients with rheumatoid arthritis and lupus, independent of steroid use, suggests the possibility that hydroxychloroquine may have a role in reducing 2 key risk factors for atherosclerosis, namely type 2 diabetes and dyslipidemia, in the general population.

Certain strengths and limitations of this study warrant mention. All data, while collected prospectively, were obtained by self-report with the limitations inherent in this approach. However, follow-up in those patients classified with incident diabetes without concomitant hypoglycemic therapy showed that hypoglycemic therapy was more often initiated in those with hydroxychloroquine never use than in those with ever use. These findings suggest that differences in self-report of diabetes by hydroxychloroquine status do not explain the observed results. Based on the age of the participants, we suspect that the majority of incident cases developed type 2 diabetes, although we cannot know this with certainty. The proportion of patients with incident diabetes not taking hypoglycemic agents during subsequent observation further substantiates this. Information on rheumatoid arthritis medications taken prior to study entry was not consistently available for all patients; thus, some patients with prior hydroxychloroquine use were classified as patients with never use; however, such misclassification would have diluted associations with hydroxychloroquine use.
While the racial homogeneity of our cohort may limit the generalizability of these findings, it is noteworthy that despite the small numbers those excluded from the present analysis due to prevalent diabetes were more likely to be non-white. Moreover, non-white race also was a significant risk factor for developing diabetes in our cohort. The use of this unique longitudinal database with prospectively collected data also allowed for detailed adjustment of covariates that may affect diabetes risk. Finally, these analyses accounted for variations in aspects of rheumatoid arthritis treatment as well as diabetes diagnosis and management during a long observation period, thereby minimizing the influence of these factors on our findings.

In conclusion, this study demonstrates a significant, dose-related association between hydroxychloroquine therapy and reduced risk of diabetes in adults with rheumatoid arthritis. Antimalarial drugs may have a role in treating rheumatoid arthritis not only to suppress synovitis but also to reduce the likelihood of developing glucose intolerance and dyslipidemia. As quality of life and life expectancy improve for patients with rheumatoid arthritis, and health care costs escalate, the use of inexpensive, safe therapies that have multiple beneficial effects is attractive.

Further prospective studies are needed to determine whether this treatment option should be considered a standard component of rheumatoid arthritis combination therapy in the future, and to evaluate the potential role of hydroxychloroquine as a preventative agent for diabetes among high-risk individuals in the general population.

Author Contributions: Dr Wasko had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wasko, Hubert, Elliott, Friis, Ward. Acquisition of data: Wasko, Hubert, Lingala, Lugen, Friis. Analysis and interpretation of data: Wasko, Hubert, Lingala, Friis, Ward. Drafting of the manuscript: Wasko, Hubert, Elliott. Critical revision of the manuscript for important intellectual content: Wasko, Hubert, Lingala, Elliott, Lugen, Friis, Ward. Statistical analysis: Hubert, Lingala, Ward. Obtained funding: Wasko, Friis, Ward. Administrative, technical, or material support: Elliott, Friis, Ward. Study supervision: Wasko, Hubert, Friis, Ward. Financial Disclosures: Dr Wasko reported being a consultant to Centocor in cardiovascular outcomes in ongoing rheumatoid arthritis clinical trials and has been a coinvestigator in multiple, institution-sponsored study of thrombomodulin markers in rheumatoid arthritis and osteoarthritis. Dr Wasko reported receiving contractual reimbursement as site principal investigator for an Aventis-sponsored clinical trial of fenofibrate in rheumatoid arthritis, ending in November 2002. Dr Wasko reported receiving contractual reimbursement as site principal investigator for rheumatoid arthritis clinical trials sponsored by Centocor, Roche, Human Genome Sciences, and Novartis. No other authors reported disclosures.

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Role of the Sponsor: Neither the Arthritis Foundation nor the National Institutes of Health was involved in the design and conduct of the study or in the collection, management, analysis, or interpretation of the data, or the preparation, review, or approval of the manuscript.

Additional Contributions: The authors dedicate this article to the memory of John Sibbey, MD, professor of medicine, Royal University Hospital, Saskatoon, Saskatchewan, whose contributions over his 15 years as an ARAMIS investigator were essential to numerous publications based on the ARAMIS cohort prior to his untimely death in 2007. Janice Sabatine, PhD, paid consultant, provided administrative and editorial contributions to the preparation of the manuscript.

REFERENCES


