Hydroxychloroquine and Glycemia in Women with Rheumatoid Arthritis and Systemic Lupus Erythematosus

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ABSTRACT. ***Objective.*** To determine the relationship between current hydroxychloroquine (HCQ) use and 2 indicators of glycemic control, fasting glucose and insulin sensitivity, in nondiabetic women with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA).

Methods. Nondiabetic women with SLE (n = 149) or RA (n = 177) recruited between 2000 and 2005 for a cross-sectional evaluation of cardiovascular risk factors were characterized by HCQ usage status. Unadjusted and multivariately adjusted mean fasting glucose, median insulin, and insulin resistance [assessed by the homeostasis model assessment (HOMA-IR) calculation] were compared among HCQ users and nonusers for disease-specific groups.

Results. More women with SLE were taking HCQ than those with RA (48% vs 18%; $p < 0.0001$; mean dose ~ 400 mg vs ~ 200 mg). For women with SLE or RA, after adjustment for age, waist circumference, disease duration, prednisone dosage, C-reactive protein, menopausal status, nonsteroidal antiinflammatory drugs, and disease-specific indicators, serum glucose was lower in HCQ users than in nonusers (SLE: 85.9 vs 89.3 mg/dl, $p = 0.04$; RA: 82.5 vs 86.6 mg/dl, $p = 0.05$). In women with SLE, HCQ use also was associated with lower $_{log}$HOMA-IR (0.97 vs 1.12, $p = 0.09$); in those with RA, no differences in $_{log}$HOMA-IR were seen. HCQ usage was not associated with fasting insulin levels in either patient group.

Conclusion. HCQ use was associated with lower fasting glucose in women with SLE or RA and also lower $_{log}$HOMA-IR in the SLE group. The use of HCQ may be beneficial for reducing cardiovascular risk by improving glycemic control in these patients. (First Release May 1 2010; J Rheumatol 2010;37:1136–42; doi:10.3899/jrheum.090994)

Key Indexing Terms:
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Diabetes mellitus (DM) is an established risk factor for atherosclerosis in the general population and in patients with systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA)[1,2]. Women with SLE or RA have a significantly higher risk of cardiovascular events than the age-matched normal population[3-5]. Recent evidence from the Framingham Heart Study demonstrates an association between impaired fasting glucose and increased risk of coronary heart disease in women who do not fulfill diagnostic criteria for diabetes[6]. Treatments for SLE and RA that maintain euglycemia may be expected to reduce the risk of incident diabetes and hence cardiovascular disease (CVD) burden.

Hydroxychloroquine (HCQ) is an antimalarial quinoline prescribed for the treatment of SLE and RA since 1955[7,8]. The drug is generally well tolerated and has low risk of toxicity with longterm use. Hypoglycemia is a rare but established side effect of quinoline therapy[9-11]. Further, in patients with RA using HCQ for more than 4 years, > 75% reduction in risk of incident diabetes has been reported[12]. However, the mechanism(s) of action of HCQ in regulating glycemia are not well understood.

Our aim was to determine the relationship between HCQ use and laboratory indicators of glycemic regulation in women with SLE or RA. Specifically, we examined the association between HCQ use and each of the following: fasting glucose, insulin, ß cell function calculated by the homeostasis model assessment (HOMA-B), and insulin resistance calculated by HOMA (HOMA-IR), as these are more sensitive measures of abnormal glucose metabolism than a diagnosis of diabetes[13]. We hypothesized that HCQ use was independently associated with lower fasting glu-

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cose, insulin, and HOMA-IR, and greater HOMA-B in women with SLE or RA.

MATERIALS AND METHODS

Patients. Women with either SLE (n = 161) or RA (n = 185) were recruited for cross-sectional studies of subclinical CVD and associated risk factors. Participants were > 18 years of age, fulfilled the American College of Rheumatology (ACR) criteria for either SLE[14,15] or RA[16], and had no history of cardiovascular events (myocardial infarction, angina, or stroke). Women with RA were recruited from the University of Pittsburgh Rheumatoid Arthritis Research Registry, a database composed of outpatients with a stated interest in participating in RA-related research[17]. Women with SLE were recruited from the Pittsburgh Lupus Registry, which includes women diagnosed with SLE who have been seen at inpatient or outpatient facilities[18]. All studies were observational; severity of disease and individual treatment courses were not connected to research participation.

During a single visit, each woman completed a standardized history (including demographic and lifestyle information) and a physical examination, and gave a fasting blood sample. Additional testing, including carotid ultrasonography or electron beam computed tomography of the coronary arteries, was completed for the parent studies[17,18]. For this analysis, patients with a diagnosis of diabetes by self-report, fasting glucose > 126 mg/dl, or reporting insulin or hypoglycemic drug use also were excluded (n = 20). Our study was approved by the Institutional Review Board of the University of Pittsburgh and all patients gave informed consent.

Outcomes. We performed a cross-sectional analysis of 326 nondiabetic women with SLE (n = 149) or RA (n = 177), comparing those taking HCQ with those not taking HCQ. Demographic data, disease measures, physical and blood assessments, and medication use were assessed separately for women with SLE and RA using equivalent protocols.

Our primary outcome measures were fasting serum glucose (mg/dl), fasting serum insulin (μU/ml), HOMA-B [defined as 20 × fasting insulin in (μU/ml)/(fasting glucose in mmol/l – 3.5)], and HOMA-IR, a calculated estimate of insulin resistance, defined as fasting glucose (mmol/l) × fasting insulin (μU/ml)/22.5[19]. Impaired fasting glucose is indicated at 100 mg/dl[20], and HOMA-IR > 2.114 is considered indicative of insulin resistance[13,21]. For the non-normally distributed variables (insulin, HOMA-B, and HOMA-IR), log transformation of data was used.

Data analysis. Descriptive statistics were used to characterize women with SLE and RA. Comparisons by HCQ usage were made using the t-test for normally distributed continuous variables and chi-squared statistics for categorical variables. Non-normally distributed variables [e.g., C-reactive protein (CRP)] were compared using nonparametric testing, and natural log transformation was used for multivariable analyses. Additionally, prednisone dose was divided into 4 categories (0, > 0 to ≤ 2.5, > 2.5 to ≤ 5, > 5 mg/day), based on clinical cutpoints of our sample and menopausal status into 3 categories (pre/perimenopause, postmenopause, postmenopause on estrogen).

In separate analyses for women with SLE and RA using general linear modeling techniques controlling for multiple variables, least-squares means of glucose, insulin, HOMA-B, and HOMA-IR were calculated for women taking HCQ and compared to women not taking HCQ. All variables significantly different between groups ($p < 0.15$ in Table 1) were initially included in the multivariable model. Guided by these results and *a priori* hypotheses based on the literature, the final models included age, disease duration, waist circumference, prednisone dose, CRP, menopausal status, and nonsteroidal antiinflammatory drug use; plus immunosuppressants and SLE Disease Activity Index (SLEDAI) for women with SLE, or nonbiologic disease-modifying antirheumatic drugs (DMARD, excluding HCQ) and tumor necrosis factor inhibitors for women with RA.

Exploratory analyses were conducted regarding associations among postmenopausal women, a dose-response relationship in women with SLE, and steroid use (by examining interactions and stratification by prednisone use). The reduced sample size and multiple covariates in these additional models limited their interpretation.

RESULTS

Characteristics of the study participants are presented in Table 2. Mean disease duration was 16 years in both groups. The women with SLE were younger than those with RA, more likely to be premenopausal, and more likely to be taking HCQ than those with RA. Of the women taking HCQ, the mean daily dose for those with SLE was 336 ± 98 mg, and for those with RA, it was 213 ± 50 mg ($p < 0.0001$).

For women with SLE, those taking HCQ had lower fasting glucose, HOMA-IR, and low-density lipoprotein (LDL) levels, and were more likely to report current daily prednisone use than those not taking HCQ (Table 1). For women with RA, those taking HCQ had higher HOMA-B and lower atherogenic ratio, and were less likely to be taking nonbiologic DMARD than those not taking HCQ.

In the multivariable models for women with SLE (Table 3), HCQ users had a significantly lower fasting glucose than the nonusers (85.9 vs 89.3 mg/dl, $p = 0.04$). In postmenopausal women, current use of hormone replacement therapy did not alter the effect of HCQ on fasting glucose levels (85.8 vs 91.2 mg/dl, $p = 0.01$); but hormone replacement therapy was associated with lower glucose in bivariate analyses (84.2 ± 8.4 vs 91.4 ± 10.6 mg/dl, $p = 0.02$). Exploratory analyses of a dose-response relationship between glucose and HCQ usage [comparing none, low (100–250 mg), and high (400 mg) doses of HCQ] were not significant. Back-transforming results of the adjusted means, for ease of clinical interpretation, suggested that HOMA-IR was lower in the HCQ users than nonusers (2.64 vs 3.06, $p = 0.09$). Stratified analyses (Tables 4a and 4b) suggest that the association between HCQ and lower fasting glucose and higher HOMA-B was present in prednisone nonusers, while the association between lower HOMA-IR was more evident among prednisone users.

In the multivariable models for women with RA (Table 3), HCQ users also had a significantly lower fasting glucose than the nonusers (82.5 vs 86.6 mg/dl, $p = 0.051$). The lower fasting glucose levels for women taking HCQ were more evident in postmenopausal women with RA (85.8 vs 91.2 mg/dl, $p = 0.01$), with no association between hormone replacement therapy and glucose in bivariate analyses (88.8 ± 10.3 vs 88.4 ± 10.3 mg/dl, $p = 0.86$). No differences in $_{log}$HOMA-IR or $_{log}$insulin by HCQ usage were seen in women with RA. Back-transforming results of the adjusted means suggested that HOMA-B was higher in the HCQ users than nonusers (235 vs 181, $p = 0.09$). Exploratory analyses showed a trend for an interaction between HCQ use and prednisone use (any/none) in multivariable models for glucose ($p = 0.02$), $_{log}$insulin ($p = 0.04$), $_{log}$HOMA-IR ($p = 0.15$), and $_{log}$HOMA-B ($p = 0.002$). Stratified analyses suggested that lower glucose may be most evident among

Table 1. Characteristics of women by HCQ status, unadjusted (mean ± SD unless otherwise noted).

	Women with SLE			Women with RA		
	+ HCQ (n = 71)	– HCQ (n = 78)	p	+ HCQ (n = 31)	– HCQ (n = 146)	p
Demographics						
Age, yrs	49.8 ± 9.9	49.8 ± 9.7	0.98	56.5 ± 9.0	58.9 ± 87.7	0.23
White, n (%)	61 (86)	69 (88)	0.64	30 (97)	138 (95)	1.00
Hypertension, n (%)	38 (54)	40 (51)	0.78	12 (39)	57 (39)	0.97
Current smoker, n (%)	8 (11)	8 (10)	0.84	1 (3)	13 (9)	0.47
Body mass index, kg/m^2	26.9 ± 5.3	28.3 ± 7.0	0.20	28.9 ± 6.3	27.5 ± 5.7	0.23
Waist circumference, cm	84.1 ± 13.3	87.0 ± 16.3	0.23	91.4 ± 13.8	90.7 ± 16.8	0.82
Hip circumference, cm	99.4 ± 12.8	103.6 ± 16.4	0.08	107.2 ± 11.6	105.2 ± 14.6	0.48
Menopausal status, n (%)			0.87			0.32
Pre/perimenopausal	27 (38)	32 (41)		5 (16)	30 (20)	
Postmenopausal	37 (52)	40 (51)		22 (71)	82 (56)	
Postmenopausal on estrogen	7 (10)	6 (8)		4 (13)	34 (23)	
College education, n (%)	43 (61)	53 (68)	0.35	13 (42)	86 (59)	0.08
Disease measures						
Disease duration, yrs	16.5 ± 6.3	16.5 ± 7.9	0.99	12.6 ± 9.3	16.3 ± 10.8	0.08
HAQ score	NA	NA	—	0.60 ± 0.52	0.78 ± 0.62	0.13
Rheumatoid factor positivity, n (%)	NA	NA	—	22 (71)	106 (75)	0.63
SLEDAI, median (IQR)	2 (0, 4)	2 (0, 2)	0.07	NA	NA	—
Laboratory measures						
Fasting glucose, mg/dl	87.1 ± 10.3	91.5 ± 10.1	0.009	85.1 ± 9.0	88.4 ± 10.0	0.09
Fasting insulin, μU/ml, median (IQR)	11.7 (9.0, 15.4)	13.4 (9.1, 18.7)	0.16	11.0 (9.2, 13.7)	11.4 (8.0, 13.9)	0.32
HOMA-B, median (IQR)	194 (122, 265)	179 (126, 241)	0.64	183 (142, 281)	158 (109, 219)	0.03
HOMA-IR, median (IQR)	2.51 (1.73, 3.55)	2.87 (1.97, 4.28)	0.046	2.22 (1.82, 3.09)	2.48 (1.71, 3.05)	0.57
ESR, mm/h, median (IQR)	10 (4, 20)	10 (5, 20)	0.69	14 (4, 28)	10 (5, 23)	0.79
CRP, mg/l, median (IQR)	2.33 (0.88, 4.67)	2.59 (0.95, 5.94)	0.65	6.04 (3.00, 9.95)	4.94 (1.67, 12.15)	0.43
Creatinine, mg/dl	0.87 ± 0.21	0.87 ± 0.35	0.98	0.81 ± 0.24	0.88 ± 0.25	0.11
Albumin, mg/dl	4.57 ± 0.49	4.55 ± 0.51	0.83	3.99 ± 0.44	3.95 ± 0.38	0.57
HDL, mg/dl	55.8 ± 18.0	52.9 ± 15.1	0.29	63.7 ± 15.6	60.5 ± 14.4	0.27
LDL, mg/dl	102 ± 32	118 ± 34	0.004	112 ± 30	123 ± 35	0.13
Triglycerides, mg/dl, median (IQR)	110 (75, 153)	113 (80, 152)	0.57	116 (94, 142)	121 (84, 156)	0.80
Total cholesterol, mg/dl, median (IQR)	183 ± 40	196 ± 42	0.06	201 ± 33	210 ± 37	0.21
Atherogenic ratio (T. chol/HDL)	3.55 ± 1.19	3.92 ± 1.14	0.06	3.27 ± 0.68	3.62 ± 0.88	0.04
Current medications						
NSAID, n (%)	31 (44)	26 (33)	0.20	24 (77)	96 (66)	0.21
Prednisone, n (%)			0.0001			0.15
0 mg/day	31 (44)	61 (78)		16 (53)	87 (60)	
> 0 – ≤ 2.5 mg/day	5 (7)	1 (1)		6 (20)	10 (7)	
> 2.5 – ≤ 5 mg/day	21 (30)	11 (14)		5 (17)	36 (25)	
> 5 mg/day	14 (20)	5 (6)		3 (10)	12 (8)	
Nonbiologic DMARD excluding HCQ, n (%)	6 (8)	11 (14)	0.28	8 (26)	76 (52)	0.008
TNF inhibitors, n (%)	NA	NA	—	7 (23)	48 (33)	0.22
Immunosuppressants, n (%)	14 (20)	12 (15)	0.49	NA	NA	—

HCQ: hydroxychloroquine; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire Disability Index; SLEDAI: SLE Disease Activity Index; IQR: interquartile range; HOMA-B: homeostasis model assessment-B cell; HOMA-IR: HOMA-insulin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NSAID: nonsteroidal antiinflammatory drug; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor; NA: not applicable.

prednisone users, while lower insulin and higher HOMA-B levels may be most evident in women not taking prednisone (Tables 4a and 4b).

DISCUSSION

In this cross-sectional study of women with SLE or RA, we found that HCQ use was significantly associated with lower fasting glucose levels. In the women with RA, calculated ß cell function (HOMA-B) was greater in HCQ users than nonusers. Calculated insulin resistance (HOMA-IR) was lower in HCQ users among women with SLE but not in those with RA. These relationships persisted after adjustment for the known covariates associated with blood glucose level. The mechanisms underlying these associations remain to be determined in mechanistic studies, but our data suggest that HCQ was not linked to improved insulin sensitivity, as HOMA-IR was not different between HCQ users and nonusers in the women with RA.

Table 2. Patient characteristics (mean ± SD unless otherwise noted).

Characteristics	SLE, n = 149	RA, n = 177
Demographics		
Age, yrs	49.8 ± 9.7	58.5 ± 10.4
White, n (%)	130 (87)	168 (95)
Hypertension, n (%)	78 (52)	69 (39)
Current smoker, n (%)	16 (11)	14 (8)
Body mass index, kg/m^2	27.6 ± 6.2	27.8 ± 5.8
Waist circumference, cm	85.6 ± 15.0	90.8 ± 16.3
Hip circumference, cm	101.6 ± 14.9	105.5 ± 14.1
Menopausal status, n (%)		
Pre/perimenopausal	59 (40)	35 (20)
Postmenopausal	77 (52)	104 (59)
Postmenopausal on estrogen	13 (9)	38 (21)
College education, n (%)	96 (64)	99 (56)
Disease measures		
Disease duration, yrs	16.5 ± 7.1	15.6 ± 10.6
HAQ score	NA	0.75 ± 0.60
Rheumatoid factor positivity, n (%)	NA	128 (74)
SLEDAI, median (IQR)	2 (0, 2)	NA
Renal involvement, n (%)	36 (24)	NA
Laboratory tests		
ESR, mm/h, median (IQR)	10 (5, 20)	10 (5, 25)
CRP, mg/l, median (IQR)	2.35 (0.94, 5.56)	4.99 (1.76, 11.50)
Creatinine, mg/dl	0.87 ± 0.29	0.87 ± 0.25
Albumin, mg/dl	4.56 ± 0.50	3.96 ± 0.39
HDL, mg/dl	54.3 ± 16.6	61.1 ± 14.6
LDL, mg/dl	110 ± 34	121 ± 34
Tryglycerides, mg/dl, median (IQR)	11 (76, 153)	118 (88, 156)
Total cholesterol, mg/dl	190 ± 42	209 ± 36
Atherogenic ratio (total cholesterol/HDL)	3.56 ± 0.86	3.74 ± 1.18
Glucose ≥ 100 mg/dl, n (%)	22 (15)	19 (11)
HOMA-IR > 2.114, n (%)	95 (64)	101 (57)
Current medications		
NSAID, n (%)	57 (38)	120 (68)
Prednisone, n (%)		
0 mg/day	92 (62)	103 (59)
> 0 – ≤ 2.5 mg/day	6 (4)	16 (9)
> 2.5 – ≤ 5 mg/day	9 (6)	11 (6)
> 5 mg/day	42 (28)	45 (26)
HCQ, n (%)	71 (48)	31 (18)
Nonbiologic DMARD, excluding HCQ, n (%)	17 (11)	84 (47)
TNF inhibitors, n (%)	NA	55 (31)
Immunosuppressants, n (%)	26 (14)	NA

SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire Disability Index; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostasis model assessment-insulin; NSAID: nonsteroidal antiinflammatory drug; HCQ: hydroxychloroquine; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor; IQR: interquartile range; NA: not applicable.

Table 3. Comparison of glucose metabolism by HCQ and disease status, by mean value adjusted for age, disease duration, waist circumference, prednisone dose, CRP, menopausal status, and NSAID; plus (a) immunosuppressants and SLEDAI for women with SLE, or (b) nonbiologic DMARD (excluding HCQ) and TNF inhibitors for women with RA.

Metabolism Factors	+ HCQ	– HCQ	p
Fasting glucose, mg/dl			
Women with SLE	85.9	89.3	0.04
Women with RA	82.5	86.6	0.051
$_{\log}$Insulin			
Women with SLE	2.53	2.64	0.18
Women with RA	2.44	2.36	0.37
$_{\log}$HOMA-B			
Women with SLE	5.40	5.37	0.78
Women with RA	5.46	5.20	0.06
$_{\log}$HOMA-IR			
Women with SLE	0.97	1.12	0.09
Women with RA	0.84	0.81	0.70

HCQ: hydroxychloroquine; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HOMA-B: homeostasis model assessment - ß cell; HOMA-IR: homeostasis model assessment-insulin; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drug; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor.

Differences in HOMA-B and HOMA-IR findings by disease may be due to a number of factors. In this observational study, HCQ usage was much more common in the women with SLE (48%), while less than 20% of the women with RA were taking HCQ; thus subtle differences in outcome measures perhaps would be detected in an RA group with a larger number of HCQ users. In addition, HCQ dosage among women with RA was much lower than in women with SLE. Disease-related distinctions such as peak age at onset, patterns of internal organ involvement, and treatment were not available for inclusion in the models but may also be influencing disease-specific results.

Postmenopausal estrogen use has been shown to lower blood glucose in older women[22]. While our findings indicate that this is true among postmenopausal women with SLE, the effect of HCQ on blood glucose levels in our cohort was independent of hormone replacement therapy.

HCQ and blood sugar. Numerous reports have suggested that antimalarials may cause a reduction in blood sugar. Scattered case reports highlight symptomatic hypoglycemia as a serious but uncommon adverse effect of HCQ in both diabetics and nondiabetics[9-11]. HCQ has been used successfully as an adjunct treatment for patients with type 2 diabetes with poor control using traditional hypoglycemic agents[23,24].

In 1994, Petri, *et al* showed that in patients with SLE, HCQ is associated with lower random glucose levels[25], and in 1999, Shojania, *et al* described a case in which the use of HCQ reduced the insulin requirements of a patient with RA and type 2 diabetes[9]. In 2007, Wasko, *et al* reported a reduced incidence of diabetes in patients with RA taking HCQ[12].

In the early 1990s, 2 studies investigating the effect of antimalarials on diabetes control in patients with non-insulin-dependent DM (NIDDM) were performed.

Table 4A. Comparison of glucose metabolism by HCQ and disease status among women not using prednisone, by mean value adjusted for age, disease duration, waist circumference, prednisone dose, CRP, menopausal status, and NSAID; plus (a) immunosuppressants and SLEDAI for women with SLE, or (b) nonbiologic DMARD (excluding HCQ) and TNF inhibitors for women with RA.

Metabolism Factors	+ HCQ	– HCQ	p
Fasting glucose, mg/dl			
Women with SLE, n = 92	83.5	89.1	0.01
Women with RA, n = 103	87.0	90.3	0.30
$_{log}$Insulin			
Women with SLE	2.53	2.54	0.93
Women with RA	2.45	2.26	0.15
$_{log}$HOMA-B			
Women with SLE	5.47	5.24	0.08
Women with RA	5.25	4.94	0.09
$_{log}$HOMA-IR			
Women with SLE	0.94	1.02	0.54
Women with RA	0.91	0.75	0.27

HCQ: hydroxychloroquine; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HOMA-B: homeostasis model assessment - ß cell; HOMA-IR: homeostasis model assessment-insulin; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drug; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor.

Table 4B. Comparison of glucose metabolism by HCQ and disease status among prednisone users, by mean value adjusted for age, disease duration, waist circumference, prednisone dose, CRP, menopausal status, and NSAID; plus (a) immunosuppressants and SLEDAI for women with SLE, or (b) nonbiologic DMARD (excluding HCQ) and TNF inhibitors for women with RA.

Metabolism Factors	+ HCQ	– HCQ	p
Fasting glucose, mg/dl			
Women with SLE, n = 57	86.1	87.0	0.74
Women with RA, n = 72	79.8	84.8	0.09
$_{log}$Insulin			
Women with SLE	2.64	2.87	0.13
Women with RA	2.30	2.36	0.70
$_{log}$HOMA-B			
Women with SLE	5.63	5.84	0.27
Women with RA	5.47	5.32	0.50
$_{log}$HOMA-IR			
Women with SLE	1.08	1.31	0.15
Women with RA	0.67	0.79	0.47

HCQ: hydroxychloroquine; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; HOMA-B: homeostasis model assessment - ß cell; HOMA-IR: homeostasis model assessment-insulin; CRP: C-reactive protein; NSAID: nonsteroidal antiinflammatory drug; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; DMARD: disease-modifying antirheumatic drug; TNF: tumor necrosis factor.

Among 38 patients with treatment-refractory NIDDM, glycemic control improved in those taking HCQ. This was not attributed to increased insulin secretion because serum C-peptide levels were unchanged[23]. An insulin clamp study in 20 human subjects with NIDDM indicated that chloroquine affects insulin metabolism both by reducing insulin clearance from the circulation and by increasing insulin secretion, the latter shown by increased C-peptide levels[26]. Our study does not address the mechanism(s) of action of antimalarials to improve glycemic control; this warrants future investigation.

Additional benefits of antimalarial therapy. Antimalarials possibly have other beneficial effects on the reduction of cardiovascular risk factors. Others have shown that HCQ use is associated with lower serum cholesterol markers[27]. In our study, women with SLE using HCQ had notably lower LDL and total cholesterol compared to nonusers. Based on their beneficial effects on risk factors for CVD (i.e., lower blood sugar, cholesterol, and other lipids, as well as decreased thromboembolism[28,29]), it would seem likely that antimalarials reduce the risk of CVD and may protect against the onset of DM. These hypotheses, however, have yet to be tested directly.

Risk factors for CVD in patients with rheumatic disease. The well known traditional cardiovascular risk factors include hypertension, smoking, male sex, advanced age, hypercholesterolemia, and diabetes. Higher fasting glucose has also been shown to be a cardiac risk factor[3]. Compared to age-matched and sex-matched control subjects, patients with SLE and RA have been shown to have a higher prevalence of hypertension and hyperlipidemia[2,30]. In patients with SLE compared to controls, an increased prevalence of diabetes has been noted; this relationship in RA is less consistently reported[31,32]. Those patients with SLE and DM may be at increased risk of developing renal impairment, neuropathy, retinopathy, and CVD — all complications that can be seen with either disease alone[33]. Therefore, decreasing the risk of hyperglycemia and/or DM in patients with SLE is very important.

Patients with SLE or RA also have disease-associated cardiovascular risk. Potential explanations for this include the effects of a chronic inflammatory milieu on the vasculature, insulin resistance associated with systemic inflammation, sedentary lifestyle, decreased lean body mass with increased relative adiposity, and increased risk of premature menopause, the latter being especially relevant in women with SLE[29,34,35].

Use of other antirheumatic drugs may alter the risk of CVD as well. For example, in patients with SLE, Doria, *et al* found that cumulative prednisone dose was associated with subclinical atherosclerosis measured by carotid ultrasound, even after adjusting for traditional Framingham cardiovascular risk factors[36]. It is not clear, however, if this relationship is due to longer disease duration, which is a known independent risk factor for subclinical atherosclerosis in these patients.

There are several potential study limitations. The cross-sectional design restricts the analysis to an association

and provides no information about causal relationships. Because this is an observational study and women were not randomized to receive HCQ, our data may be biased based on confounding by indication, with fewer "sick" patients receiving HCQ, although we did adjust for use of other disease-modifying therapy (for RA) and concurrent immunosuppressive drugs (for SLE). Analyses were also completed on each disease group based on concurrent steroid usage status. Lean body mass and physical activity level, which may influence glucose metabolism, were not measured in all patients. Finally, the small number of participants may have precluded reaching statistical significance in some of the analyses, particularly given the small proportion of RA women using HCQ and their low mean daily dose.

HCQ is a safe and inexpensive medication used frequently in treatment of SLE and RA. In addition to direct benefits in managing rheumatic diseases, HCQ is associated with lower fasting glucose levels in women with SLE or RA. HCQ is also associated with lower insulin resistance in women with SLE. These results are consistent with our report of a protective association between HCQ use and incident DM in patients with RA[12]. It is possible that HCQ could also reduce the risk of coronary heart disease among subjects with diabetes by improving glycemic control and dyslipidemia and reducing risk of thrombosis, although this has not yet been directly studied. Future work is warranted to identify specific patient subsets that may be particularly responsive to HCQ's beneficial effects on glycemia.

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