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Original Article

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Effects of Anti-Malarial Drug, Hydroxychloroquine, on Glucose and Lipid Metabolism in Japanese Population

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Abstract

Background: Hydroxychloroquine (HCQ) is a synthetic anti-malarial drug and has been used for the treatment of rheumatic diseases. Recently, HCQ has been reported to improve lipid and glucose metabolism in patients with rheumatic diseases. However, effects of HCQ on lipid and glucose metabolism in Japanese remain unknown.

Methods: We picked up patients who had been prescribed HCQ for 1 month or longer between September 2015 and August 2018. We compared the data at baseline and at 1 - 11 months after the start of HCQ. We excluded patients who discontinued to take HCQ due to adverse reaction, and patients who had taken daily more than 20 mg of prednisolone with HCQ.

Results: We found 40 patients, and excluded nine patients who discontinued to take HCQ due to adverse reactions and five patients who had taken daily more than 20 mg of prednisolone in addition to HCQ, and we analyzed 26 patients. Twenty-two systemic lupus erythematosus (SLE) patients and 4 rheumatoid arthritis (RA) patients had been prescribed HCQ. Hemoglobin A1c (HbA1c) showed a significant decrease and tendency to decrease at 5 and 6 months after the start of HCQ, respectively. At other time points, HbA1c showed non-significant decrease. Serum triglyceride showed a significant decrease at 1, 3, 7, 8 and 11 months after the start of HCQ. At other time points, serum triglyceride showed non-significant decrease. Serum high-density lipoprotein-cholesterol (HDL-C) did not show any significant changes at every time point. Serum low-density lipoprotein-cholesterol (LDL-C) showed a significant decrease at 2 months after the start of HCQ and showed tendency to decrease after 7 and 10 months. At other time points, serum LDL-C showed non-significant decrease. Serum non-HDL-C showed a significant decrease at 2, 3 and 7 months after the start of HCQ and showed tendency to decrease after 1 and 5 months. At other time points, serum non-HDL-C showed non-significant decrease.

Conclusion: HCQ was associated with reduction of HbA1c, serum triglyceride, LDL-C and non-HDL-C levels in SLE and RA patients.

Keywords: Diabetes; Hydroxychloroquine; Serum lipids; Systemic lupus erythematosus

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Introduction

Hydroxychloroquine (HCQ) is a synthetic anti-malarial drug and has been used for the treatment of rheumatic diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). HCQ has been proved to play its role in immune regulation through a variety of mechanisms, including inhibition of autophagy, antigen presentation and cytokine chemotaxis. HCQ also reduces the production of pro-inflammatory cytokines, inhibits matrix metalloproteinases, blocks T- and B-cell receptors and participates in toll-like receptor signaling [1, 2]. Recently, HCQ has been reported to improve lipid and glucose metabolism, which may help reduce the high cardiovascular risk in SLE patients [3]. However, effects of HCQ on lipid and glucose metabolism in Japanese remain unknown. Therefore, we retrospectively studied the changes in serum lipid and hemoglobin A1c (HbA1c) levels after the start of HCQ in SLE and RA patients who had been prescribed HCQ.

Materials and Methods

This study was approval by the Institutional Ethics Committee in National Center for Global Health and Medicine (NCGM-G-003045), and was also performed in accordance with the Declaration of Helsinki.

The recruitment of studied subjects was shown in Figure 1. Briefly, we picked up patients who had been prescribed HCQ for 1 month or longer between September 2015 and August 2018 based on medical charts. We compared the data at

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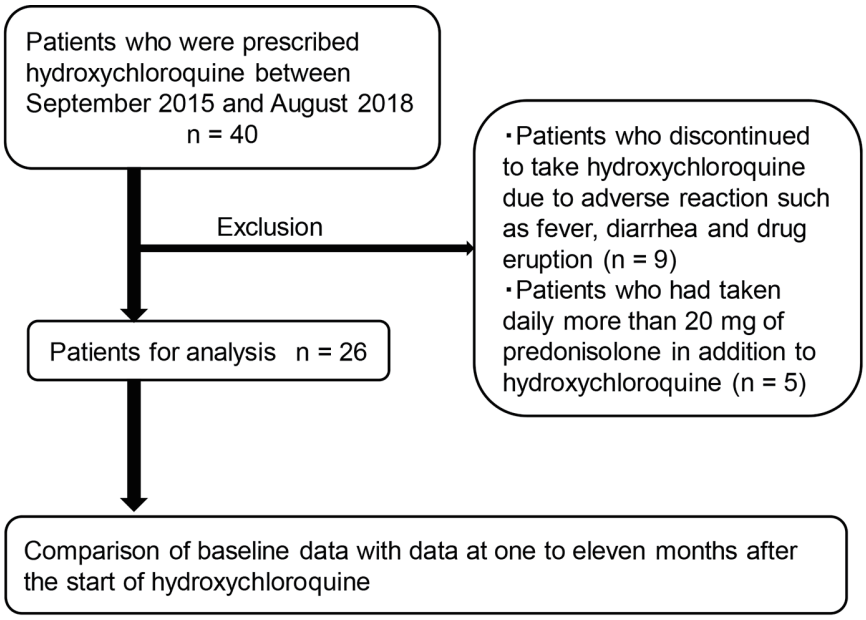

Figure 1. The recruitment of studied subjects.

baseline and at 1 - 11 months after the start of HCQ. We excluded patients who discontinued to take HCQ due to adverse reactions such as fever, diarrhea and drug eruption, and also excluded patients who had taken daily more than 20 mg of prednisolone in addition to HCQ.

Comparison of the variables determined before and after was analyzed by a paired Student's *t*-test. All data are expressed as mean ± standard deviation (SD). $P < 0.05$ and $P < 0.1$ were considered to be statistically significant and to show tendency, respectively.

Results

We found 40 patients who had been prescribed HCQ for 1 month or longer between September 2015 and August 2018, and excluded nine patients who discontinued to take HCQ due to adverse reactions and five patients who had taken daily more than 20 mg of prednisolone in addition to HCQ (Fig. 1). Therefore, we analyzed 26 patients. Clinical data of studied subjects were shown in Table 1. Twenty-two SLE patients and four RA patients had been prescribed HCQ. Three patients with diabetes and seven patients with dyslipidemia were included in this study. Daily dose of HCQ and other medication at baseline were shown in Table 2. Twenty-two patients had taken prednisolone, and mean daily dose was 6.5 mg. Two diabetic patients had taken oral anti-diabetic drugs, and six and two dyslipidemia patients had taken statin and fibrate, respectively. During the study period, decrease of daily dose of anti-diabetic drugs, statin and fibrate were observed; however, increase of daily dose

Table 1. Clinical Data at Baseline (n = 26)

Anthropometric data	
Sex (female, n (%))	22 (84.6%)
Age (years, mean ± SD)	46 ± 16
Body height (cm, mean ± SD)	159.9 ± 6.3
Body weight (kg, mean ± SD)	51.8 ± 4.6
Body mass index (kg/m^2, mean ± SD)	20.8 ± 2.4
Rheumatic diseases	
Systemic lupus erythematosus (n (%))	22 (84.6%)
Rheumatoid arthritis (n (%))	4 (15.4%)
Metabolic diseases	
Diabetes (n (%))	3 (11.5%)
Dyslipidemia (n (%))	7 (26.9%)

SD: standard deviation.

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Table 2. Daily Dose of Hydroxychloroquine and Other Medication at Baseline

Daily dose of hydroxychloroquine (mg, mean ± SD)	284.6 ± 67.5
For rheumatic diseases	
Prednisolone	
Patients who had taken prednisolone (n (%))	23 (88.5%)
Daily dose (mg)	6.5 ± 3.5
Immunosuppressants (n (%))	7 (26.9%)
For diabetes	
Oral anti-diabetic drugs (n (%))	2 (7.7%)
Insulin (n (%))	0 (0%)
For dyslipidemia	
Statin (n (%))	6 (23.1%)
Fibrate (n (%))	2 (7.7%)

SD: standard deviation.

and additional administration of such drugs were not observed.

Changes in HbA1c were shown in Table 3. HbA1c showed a significant decrease and tendency to decrease at 5 and 6 months after the start of HCQ, respectively. At other time points, HbA1c showed non-significant decrease.

Changes in serum triglyceride were shown in Table 4. Serum triglyceride showed a significant decrease at 1, 3, 7, 8 and 11 months after the start of HCQ. At other time points, serum triglyceride showed non-significant decrease. Changes in serum high-density lipoprotein-cholesterol (HDL-C) were shown in Table 5. Serum HDL-C did not show any significant changes at every time point.

Changes in serum low-density lipoprotein-cholesterol (LDL-C) were shown in Table 6. Serum LDL-C showed a significant decrease at 2 months after the start of HCQ and showed tendency to decrease after 7 and 10 months. At other time points, serum LDL-C showed non-significant decrease. Changes in serum non-HDL-C were shown in Table 7. Serum non-HDL-C showed a significant decrease at 2, 3 and 7 months after the start of HCQ and showed tendency to decrease after 1 and 5 months. At other time points, serum non-HDL-C showed non-significant decrease.

Discussion

The metabolic syndrome (MetS) is now recognized as a chronic proinflammatory state that aggravates insulin resistance. MetS and atherosclerosis are more prevalent in patients with SLE and RA [4]. There is an urgent need for clinical trials to examine both the lipid-lowering and inflammatory hypotheses of atherosclerosis in SLE and RA. Novel targeted therapies in development may also have a major impact on future coronary heart disease risk in rheumatic diseases. Dysregulation of cytokines and adipokines is a common feature in both SLE and MetS, suggesting a complex relationship among autoimmunity, obesity, inflammation and atherosclerosis [5]. While lifestyle modifications and targeting dyslipidemia, hyperten-

Table 3. Change of HbA1c After the Start of Hydroxychloroquine

Month	n	Values at baseline	Values after hydroxychloroquine use	P value
1	11	5.91 ± 0.60	5.87 ± 0.54	0.397
2	11	5.83 ± 0.59	5.75 ± 0.48	0.221
3	10	6.02 ± 0.50	5.92 ± 0.44	0.348
4	11	5.88 ± 0.62	5.74 ± 0.55	0.202
5	7	5.99 ± 0.57	5.74 ± 0.41	0.075
6	9	5.91 ± 0.69	5.66 ± 0.47	0.048
7	8	6.01 ± 0.55	5.76 ± 0.32	0.154
8	7	5.73 ± 0.72	5.50 ± 0.51	0.331
9	7	5.86 ± 0.77	5.71 ± 0.50	0.441
10	6	5.80 ± 0.76	5.52 ± 0.50	0.164
11	7	5.97 ± 0.64	5.70 ± 0.46	0.184

HbA1c: hemoglobin A1c.

Table 4. Change of Serum Triglyceride (mg/dL) After the Start of Hydroxychloroquine

Month	n	Values at baseline	Values after hydroxychloroquine use	P value
1	12	101.0 ± 27.1	93.7 ± 26.8	0.005
2	10	102.3 ± 27.9	99.3 ± 30.5	0.657
3	11	102.6 ± 21.7	90.1 ± 24.5	0.011
4	13	99.2 ± 25.7	96.2 ± 32.5	0.618
5	10	101.8 ± 19.7	96.5 ± 16.2	0.228
6	9	88.1 ± 20.7	81.7 ± 20.6	0.318
7	9	105.2 ± 22.8	88.8 ± 17.6	0.006
8	8	98.0 ± 28.7	81.5 ± 24.1	0.045
9	9	93.2 ± 25.2	88.0 ± 18.8	0.438
10	9	97.2 ± 27.0	95.0 ± 30.5	0.876
11	9	104.1 ± 22.2	87.6 ± 17.2	0.022

Table 5. Change of Serum HDL-C (mg/dL) After the Start of Hydroxychloroquine

Month	n	Values at baseline	Values after hydroxychloroquine use	P value
1	13	59.5 ± 22.9	59.1 ± 21.5	0.722
2	11	59.2 ± 24.5	57.8 ± 24.4	0.393
3	12	61.2 ± 23.2	61.0 ± 23.0	0.908
4	14	58.2 ± 21.3	60.4 ± 21.7	0.104
5	10	60.7 ± 23.6	63.3 ± 21.8	0.164
6	10	61.6 ± 22.4	59.1 ± 24.4	0.231
7	10	66.4 ± 21.8	64.9 ± 20.9	0.696
8	8	62.9 ± 24.5	62.8 ± 22.9	0.955
9	10	63.2 ± 22.9	67.5 ± 21.6	0.217
10	10	61.8 ± 22.5	65.4 ± 22.9	0.287
11	10	65.3 ± 21.1	65.7 ± 22.5	0.846

HDL-C: high-density lipoprotein-cholesterol.

Table 6. Change of Serum LDL-C (mg/dL) After the Start of Hydroxychloroquine

Month	n	Values at baseline	Values after hydroxychloroquine use	P value
1	14	157.4 ± 102.6	141.5 ± 138.0	0.382
2	13	179.9 ± 100.3	134.8 ± 68.1	0.009
3	13	143.2 ± 64.6	131.7 ± 58.1	0.373
4	16	173.9 ± 101.5	149.6 ± 128.1	0.133
5	10	151.0 ± 75.2	115.9 ± 47.2	0.132
6	12	190.8 ± 106.5	176.8 ± 127.1	0.551
7	11	133.1 ± 65.9	101.5 ± 37.3	0.099
8	9	182.9 ± 132.5	158.1 ± 125.1	0.291
9	12	180.8 ± 108.7	155.6 ± 95.5	0.558
10	11	180.3 ± 120.3	134.0 ± 52.3	0.098
11	11	141.8 ± 69.8	125.4 ± 70.7	0.392

LDL-C: low-density lipoprotein-cholesterol.

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Table 7. Change of Serum Non-HDL-C (mg/dL) After the Start of Hydroxychloroquine

Month	n	Values at baseline	Values after hydroxychloroquine use	P value
1	13	135.2 ± 26.9	120.8 ± 20.2	0.051
2	11	143.3 ± 22.8	127.8 ± 27.4	0.038
3	12	132.7 ± 28.3	119.0 ± 23.9	0.008
4	14	133.7 ± 26.0	126.5 ± 24.3	0.157
5	9	131.4 ± 25.9	119.8 ± 17.6	0.074
6	10	127.8 ± 24.2	122.4 ± 22.2	0.579
7	10	134.0 ± 29.1	111.7 ± 15.1	0.011
8	8	129.5 ± 26.2	115.9 ± 18.4	0.202
9	10	131.9 ± 26.6	122.7 ± 19.2	0.278
10	10	133.2 ± 24.9	124.5 ± 25.7	0.361
11	10	133.0 ± 28.1	120.8 ± 23.6	0.164

HDL-C: high-density lipoprotein-cholesterol.

sion and diabetes is essential, there is little information on the efficacy and safety of HCQ in alleviating insulin resistance in SLE [5]. We observed a significant decrease of HbA1c at 6 months after the start of HCQ and decrease of HbA1c at every time point. HCQ has been reported to play a role in improving obesity-induced lipotoxicity and insulin resistance though the peroxisome proliferator-activated receptor gamma pathway in obese mice [6]. A systematic review and meta-analysis which studied metabolic and cardiovascular benefits of HCQ in patients with RA showed that diabetes incidence was lower for HCQ ever users than never users (hazard ratio (HR) 0.59 (95% confidence interval (CI) 0.49 to 0.70)) [7]. HCQ may improve glucose metabolism due to amelioration of insulin resistance by reduced inflammatory state.

The meta-analysis using RA patients showed that the mean differences (MDs) between HCQ users and non-users in levels of total cholesterol (TC), LDL-C, HDL-C and triglyceride were -9.8 (95% CI -14.0 to -5.6), -10.6 (95% CI -14.2 to -7.0), +4.1 (95% CI 2.2 to 6.0) and -19.2 (95% CI -27.2 to -11.1), respectively [7]. Although serum HDL-C did not show any significant changes at every time point in present study, serum triglyceride, LDL-C and non-HDL-C showed a significant decrease at several time points and showed a decrease at every time point after the start of HCQ as compared with baseline. In a systematic review and meta-analysis which studied effects of chloroquine (CQ) or HCQ on serum lipids in SLE patients, compared with the control group, TC, triglyceride, LDL-C, very low-density lipoprotein (VLDL)-C were associated with a significant decrease, respectively (weighted the mean difference (WMD) = -21.40 mg/dL, 95% CI -27.62 to -15.18, P < 0.00001), (WMD = -29.07 mg/dL, 95% CI -45.28 to -12.86, P = 0.0004), (WMD = -16.25 mg/dL, 95% CI -28.82 to -3.68, P = 0.01), (WMD = -6.41 mg/dL, 95% CI -12.39 to 0.44, P = 0.04); however, the change of HDL-C did not reach statistically significance (WMD = 4.42 mg/dL, 95% CI -1.21 to 10.06, P = 0.12), which completely agreed with our results [8].

The mechanism of HCQ or CQ decreasing the serum lipid among SLE patients remains unclear. Chen et al reported that CQ treatment of rat cells in culture results in the increase of hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase activity [9], which was a rate-limiting enzyme in the process of cholesterol synthetize in hepatocytes. After CQ administration, the hepatic activities of lysosomal enzymes were increased and cholesterol saturation of bile decreased by 22% in rat [10]. Sachet et al reported that CQ can up-regulate LDL-receptor in SLE [11].

Insulin resistance induced by inflammation in SLE and RA increases activity and expression of hormone-sensitive lipase (HSL) in adipose tissue, which catalyzes the breakdown of TG, releasing free fatty acids (FFA) [12]. Increased FFA entry to liver may elevate hepatic production of VLDL. Relative insulin deficiency also decreases the activity of lipoprotein lipase (LPL), the rate-limiting enzyme of the catabolism of TG-rich lipoproteins [13]. Therefore, reduced LPL activity increases TG and VLDL. HCQ may improve inflammatory state, which normalizes HSL and LPL function and results in improvement of dyslipidemia. However, the underlying mechanisms for HCQ-induced improvement of dyslipidemia should be elucidated in the future.

The present study has limitations. First, the number of studied subjects was small. Second, since this study was retrospective and based on medical charts, lack of data might influence the results. A more detailed prospective study is recommended.

Conclusion

HCQ was associated with reduction of HbA1c, serum triglyceride, LDL-C and non-HDL-C levels in SLE and RA patients.

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Authors have no financial disclosures to report.

Conflict of Interest

The authors declare that they have no conflict of interest concerning this article.

Informed Consent

Not applicable.

Author Contributions

YM and HY designed the research. KH, NT and TK collected data. HY analyzed data, and HY wrote the paper. All authors read and approved the final paper.

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