Supplemental hydroxychloroquine therapy regulates adipokines in patients with systemic lupus erythematosus with stable disease

Risa Wakiya1 · Kiyo Ueeda1 · Hiromi Shimada1 · Shusaku Nakashima1 · Tomohiro Kameda1 · Nobuyuki Miyatake2 · Mikiya Kato1 · Taichi Miyagi1 · Koichi Sugihara1 · Mao Mizusaki1 · Rina Mino1 · Norimitsu Kadowaki1 · Hiroaki Dobashi1

Received: 17 January 2022 / Revised: 19 June 2022 / Accepted: 28 June 2022 / Published online: 18 July 2022
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Abstract

Background In patients with systemic lupus erythematosus (SLE), a higher frequency of atherosclerotic lesions is associated with poor prognosis. Hydroxychloroquine (HCQ) has been reported to improve the lifespan and the prognosis of dyslipidaemia in patients with SLE, but the mechanism is unclear. We investigated the effect of supplemental HCQ treatment on the levels of serum cytokines associated with atherosclerosis in patients with stable SLE.

Methods Patients with SLE who received supplemental HCQ and maintained low disease activity between January 2016 and September 2020 were included in this study. Disease activity was assessed using Safety of Estrogens in Lupus National Assessment-SLE Disease Activity Index, Cutaneous Lupus Erythematosus Disease Area and Severity Index, and Lupus Low Disease Activity State. Serum complement titres, anti-dsDNA antibodies, and serum cytokines (adiponectin, resistin, and leptin) were analyzed before and after HCQ treatment.

Results Forty-one patients (4 males and 37 females, mean age 41.3 ± 13.2 years) were included. Serum adiponectin levels were significantly increased after 3 months of HCQ treatment compared to baseline, and serum resistin levels were significantly reduced. The change in serum resistin level after HCQ administration was correlated with a significant reduction in serum TNF-α, interleukin (IL)-6, IL-8, and IL-1RA levels.

Conclusions Supplemental HCQ treatment in patients with SLE improved adipokine levels. HCQ may improve prognosis by controlling disease activity in SLE and reducing risk factors for atherosclerosis.

Key Points

- Hydroxychloroquine has been reported to improve the prognosis of dyslipidaemia in patients with SLE, but the underlying mechanism is unclear.
- In this study, hydroxychloroquine improved adipokine levels in patients with SLE, implicating adipokines as a potential mechanism underlying the benefit of hydroxychloroquine on dyslipidaemia.
- Supplemental hydroxychloroquine should be considered in patients with SLE harboring lipid abnormalities and risk factors for atherosclerosis.

Keywords Adipokines · Adiponectin · Hydroxychloroquine · Leptin · Resistin · Systemic lupus erythematosus

Background

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder of the connective tissue characterized by autoantibodies and immune complexes; remission and flares; and highly variable clinical presentation, disease course, and prognosis [1, 2]. Renal involvement and cardiovascular disease (CVD) are important causes of mortality in SLE [2, 3]. SLE is an independent risk factor for CVD due to both traditional and disease-related risk factors such as
persistent disease activity, lupus nephritis (LN), the presence of antiphospholipid antibodies and the use of glucocorticoids [4, 5]. Furthermore, higher frequencies of atherosclerotic risk factors, such as hypertension and dyslipidaemia, are associated with poor prognosis in SLE [3, 6].

Hydroxychloroquine (HCQ) is recommended for SLE treatment unless there is a clear contraindication [4]. HCQ improves skin symptoms and arthritis as well as prevents SLE flare-ups, organ damage and cardiovascular events and reduces the risk of developing neuropsychiatric lupus [2]. In addition, HCQ has a favorable effect on lipid levels [7–9] and reduces insulin resistance [10, 11] and the risk of thrombosis [12, 13]. It has also been shown to increase survival in patients with SLE [13, 14]. These reports suggest that HCQ may modulate serum cytokines and adipokines associated with atherosclerosis in patients with SLE; however, no study has investigated changes in the serum levels of cytokines and adipokines after HCQ administration for SLE.

HCQ was first approved for the treatment of SLE in Japan in July 2015; since then, because of the reported beneficial effects of HCQ for SLE, it has been prescribed as an additional treatment for many patients with SLE in Japan according to the recommendations [4]. We considered that it might be possible to study the effect of HCQ on cytokines related to atherosclerosis in patients with SLE on maintenance therapy, given that additional administration of HCQ would less likely affect the suppressive effect of HCQ on disease activity. In this study, we investigated the effects of HCQ therapy on serum adipokine levels in patients with SLE.

Methods

Patients

This was a single-center exploratory study. We enrolled subjects who were diagnosed with SLE using the Systemic Lupus Collaborating Clinics criteria [15] and who began HCQ treatment for the first time between January 2016 and March 2020. Prior to enrolment, all patients had a ≥3-month history of low disease activity, defined as (i) a Safety of Estrogens in Lupus National Assessment (SELENA)-SLE Disease Activity Index (SLEDAI) score of ≤8 with no activity in major organ systems, such as renal involvement, neuropsychiatric SLE, cardiopulmonary involvement, and vasculitis; (ii) current treatment with prednisolone or an equivalent dose of ≤10 mg per day; and (iii) well-tolerated treatment with maintenance doses of other immunosuppressant. Pregnant women and patients who changed glucocorticoid doses or immunosuppressant after starting HCQ treatment were excluded from the study. We also excluded patients not currently in complete renal remission [16], regardless of LN history. Informed consent was obtained from all participants. The study was approved by the ethical committee of Kagawa University (2020–003).

Treatment and outcomes

Patients were administered oral HCQ sulfate (Plaquenil; Sanofi-Winthrop, Paris, France) continuously for at least 3 months. HCQ was administered at a dose based on the patients’ ideal body weight (IBW) calculated using the modified Broca’s method: 200 mg daily for patients with IBW < 46 kg, 200 and 400 mg on alternate days for IBW ≥ 46 and < 62 kg and 400 mg daily for IBW ≥ 62 kg.

The primary outcome was change in adipokine levels after 3 months of HCQ treatment. The secondary outcome was factors associated with a change in adipokine levels.

Clinical parameters (age, sex, body mass index (BMI), immunological biomarkers, disease activity indices and skin scores) were recorded before and after HCQ treatment. Disease activity was evaluated using the SELENA-SLEDAI 2011 criteria [17] and the Lupus Low Disease Activity State criteria [18]. Cutaneous disease activity was evaluated using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) [19]. Immunological activity was determined by measuring the serum levels of complement factors (C3, C4, and CH50), anti-double-stranded DNA (dsDNA) antibodies and total white blood cell, lymphocyte, and platelet counts. Serum adiponectin was measured using ELISA (Human Total Adiponectin/Acrp30 Quantikine ELISA Kit; R&D Systems, USA). In the serum, leptin and resistin levels were determined with Simple Plex, an integrated immunoassay system for rapid and sensitive detection of targeted protein antigens across multiple biological sources. Simple Plex assays consisting of a disposable microfluidic cartridge and an automated analyzer, the Ella instrument, were performed according to the manufacturer’s instructions (Protein Simple, CA, USA). In addition, we measured the levels of serum cytokines (TNF-α, interleukin (IL)-6, IL-8, MCP-1, MIP-1α, IL-1RA, and IL-2) reported to be associated with the pathogenesis of SLE using a multiplex immunoassay (Luminex Assay, R&D Systems) and analyzed the relationship with changes in serum adipokine levels.

Statistical analysis

Normally distributed quantitative variables were expressed as means ± standard deviation, whereas nonparametric distributions were represented as medians (interquartile range or ranges). Comparisons between different groups were performed using Wilcoxon’s rank-sum test. Immunological biomarkers and proinflammatory adipokine levels were compared using Wilcoxon’s signed-rank test for non-normally distributed data. The association of adipokine levels with clinical variables and inflammatory cytokine levels was
determined by correlation analyses (Pearson’s correlation coefficient). The association between the rate of change in the levels of adipokines and biomarkers was analyzed using analysis of covariance and partial correlation analysis to remove the effects of age and BMI. All P-values were two-sided, and a P-value of <0.05 was considered significant. The data were analyzed using JMP® 15.2.1 software (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics and serum levels of adipokines

Forty-one patients (4 males and 37 females, with a mean age of 41.3 ± 13.2 years) on treatment regimens including glucocorticoids and immunosuppressive drugs other than HCQ were included. Table 1 summarizes the clinical and immunological details of the included patients with SLE.

Serum leptin levels were significantly higher in patients with SLE who received glucocorticoids than in those who did not and were higher in patients with higher BMI than in those with lower BMI (P = 0.0254 and P = 0.005, respectively; Table 2).

Adiponectin levels were negatively correlated with complement factors C3 and C4 (r = −0.33, P = 0.0357 and r = −0.39, P = 0.0116, respectively), whereas leptin was positively correlated with C3 and CH50 levels (r = 0.42, P = 0.0063 and r = 0.35, P = 0.0252, respectively). There was no significant relationship between SELENA-SLEDAI and dsDNA antibodies and serum adipokine levels. These results are shown in Table 2 and Online Resource 1.

Serum adipokine levels after HCQ treatment

Serum adiponectin levels significantly increased, and serum resistin levels significantly decreased 3 months after supplemental HCQ administration compared to their values at baseline. No significant changes were observed in serum leptin levels (Fig. 1). Table 3 shows serum adipokine and serum cytokine levels before and after treatment with HCQ and changes following the administration of supplemental HCQ.

Next, we analyzed the association between the change in adipokine levels after HCQ administration and clinical and immunological parameters. Changes in these adipokines by HCQ treatment were not associated with the presence of hypocomplementemia. However, the rate of change in leptin levels was negatively correlated with the change in anti-dsDNA antibody titres (Online Resource 2).

There was also no significant association between changes in adipokine levels and the SELENA-SLEDAI score, skin involvement, or renal involvement (Table 4, Online Resource 2). On the other hand, serum TNF-α, IL-6, and IL-1RA levels significantly decreased 3 months after HCQ treatment compared to their levels at baseline (Online Resource 3).

Among the adipokines, change in the serum resistin level after HCQ administration was correlated with a significant reduction in serum TNF-α, IL-6, IL-8, and IL-1RA levels (Table 5). A partial correlation analysis adjusted for age and BMI revealed a weak negative correlation between the rate

| Table 1 Characteristics of patients with SLE enrolled in the study |
|---------------------------------------------------------------|
| Characteristics                  | N = 41, no. (%) |
|----------------------------------|----------------|
| Female, no. (%)                  | 37 (90)        |
| Age, years, mean ± SD            | 41.3 ± 13.2    |
| Disease duration, years, mean ± SD| 14.9 ± 11.3    |
| BMI                              | 22.4 ± 3.5     |
| Past involvement                 |                |
| Renal involvement                | 18 (44)        |
| NPSLE                            | 3 (7)          |
| Complications                    |                |
| APS                              | 8 (20)         |
| Dyslipidaemia                    | 1 (2)          |
| Diabetes                         | 1 (2)          |
| Hypertension                     | 8 (20)         |
| Concomitant immunosuppressive treatments |            |
| Prednisone                       | 34 (83)        |
| No. (%)                          | 4.5 (1–10)     |
| Median dosage, mg/day (range)    |                |
| Disease activity, median, range   |                |
| SELENA-SLEDAI score              | 4.0, 0–8       |
| Current skin involvement         | 24 (59)        |
| CLASI activity score             | 2.5, 0–9 (n = 24) |
| CLASI damage score               | 0, 0–5 (n = 24) |
| Anti-dsDNA positive, no. (%)     | 15 (37)        |
| Anti-dsDNA, median, range        | 5.4, 5–82.8    |
| Low complement, no. (%)          | 20 (49)        |
| C3, mg/dl                        | 78, 40–150     |
| C4, mg/dl                        | 14, 2–33       |
| CH50, U/ml                       | 34.1, 14–57.5  |
| White blood cells, /μl           | 5000, 1460–7630|
| Lymphocytes, /μl                 | 1052, 349–3304 |
| Platelets, × 10^4/μl             | 20.8, 6.7–32.1 |
| LLDAS, no. (%)                   | 25 (61)        |
| Clinical remission on treatment, no. (%) | 4 (10) |

Anti-dsDNA positive means that anti-dsDNA titre increases to >12 IU/ml

Low complement means that C3, C4, or CH50 level decreases to <68 mg/dl, 12 mg/dl, or 30 U/ml, respectively

APS, anti-phospholipid antibody syndrome; BMI, body mass index; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SD, standard deviation; SLE, systemic lupus erythematosus; NPSLE, neuropsychiatric SLE; LLDAS, Lupus Low Disease Activity State
of change in adiponectin and the rate of change in VEGF; however, the increase in adiponectin and leptin levels was not correlated with a change in the levels of other cytokines (Table 5).

**Discussion**

Adipose tissue inflammation is associated with insulin resistance and lower production of adiponectin. Wasko et al. found that HCQ improves both beta-cell function and insulin sensitivity in healthy subjects [10]. HCQ significantly increased adiponectin levels, indicating a possible anti-inflammatory effect in adipose tissue. In addition, adiponectin has been shown to impact insulin sensitivity [20–22]. In addition to the results of a study by Toledo et al. [11], these findings suggest that the mechanism by which HCQ affects glucose metabolism is that adipose tissue responds to HCQ treatment through changes in inflammatory cytokines and adipokines, which in turn affect glucose metabolism through cross-talk among organs.

Some previous studies have reported elevated serum adiponectin, leptin, and resistin levels in patients with SLE compared with healthy subjects [23–27], whereas some studies have reported no difference in these levels between patients with SLE and healthy subjects [28–30]. Therefore, there is no consensus on whether adipokines are elevated in SLE. However, it has been reported that serum adiponectin and serum resistin as well as urinary adiponectin levels are elevated in patients with SLE with renal involvement compared to those without renal involvement [23, 24, 26, 31, 32]. These findings indicate that adiponectin and resistin are useful markers associated with LN. In this study, there was no significant difference in adipokine levels between patients with and without pre-existing renal involvement. Since only patients with LN who were in remission were included in this study, no significant difference in serum adipokine levels was observed between patients with LN and those without LN.

The relationship between adipokines and disease activity in patients with SLE other than in those with LN has also been reported in several studies. In addition, serum adiponectin levels have been positively correlated with disease activity and negatively correlated with serum C3 levels [26, 28]. Additionally, serum leptin levels were negatively correlated with disease activity and anti-dsDNA antibodies and positively correlated with hypocomplementemia [28]. In this study, we also showed an association between adiponectin or leptin and complement factors as in previous reports. On the other hand, there are reports that there is no association between SLE disease activity and adipokines [24, 27].

Resistin is an inflammatory regulator that acts downstream of inflammation [33, 34]. Upon stimulation with resistin, macrophage cells, peripheral blood mononuclear cells and hepatic stellate cells increase the release of TNF-α, IL-6, IL-1β, IL-12, IL-8, and MCP-1 via NF-κB [35–37], which promotes an inflammatory response. However, several endogenous substances, such as proinflammatory cytokines, also upregulate resistin expression [33, 36]. Thus, resistin and proinflammatory cytokines are related, and circulating...
resistin levels are positively correlated with proinflammatory cytokines such as CRP, TNF-α, and IL-6 in type 2 diabetes, rheumatoid arthritis, chronic kidney disease, sepsis, and coronary atherosclerosis [38, 39]. In SLE, a correlation between serum resistin level and serum TNF-α and IL-6 levels has been demonstrated [30, 40], but reports are scarce.
## Table 4: Association between clinical parameters and changes in adipokine level

| Rate of change in cytokines | Adiponectin (%) | Leptin (%) | P | Adjusted P | Resistin (%) | P | Adjusted P |
|-----------------------------|-----------------|------------|---|------------|--------------|---|------------|
| **BMI > 22**                |                 |            |   |            |              |   |            |
| +                           | 20              | 17.83 (7.61, 52.76) | 0.4113 | 0.7833 | −4.22 (−28.21, 8.19) | 0.7764 | 0.1109 | −16.97 (−39.42, −4.02) | 0.4407 | 0.5149 |
| −                           | 21              | 11.57 (1.97, 32.18) | −13.92 (−35.08, 22.45) | −26.05 (−46.38, −14.46) |
| **Glucocorticoids**         |                 |            |   |            |              |   |            |
| +                           | 34              | 16.03 (8.28, 47.91) | 0.3960 | 0.5884 | −7.50 (−30.45, 9.53) | 0.8868 | 0.4833 | −20.00 (−43.60, −3.35) | 0.1651 | 0.1106 |
| −                           | 7               | 6.92 (2.18, 47.49) | −6.30 (−59.10, 44.49) | −34.43 (−49.06, −20.39) |
| **History of lupus nephritis** |           |            |   |            |              |   |            |
| +                           | 18              | 17.83 (8.15, 51.05) | 0.3510 | 0.5549 | −2.15 (−29.15, 11.98) | 0.6815 | 0.6628 | −30.57 (−49.96, −14.65) | 0.0951 | 0.1429 |
| −                           | 23              | 11.34 (4.13, 41.82) | −7.50 (−39.05, 10.55) | −18.69 (−40.91, −2.70) |
| **Decrease in SLEDAI score** |           |            |   |            |              |   |            |
| +                           | 21              | 12.10 (9.89, 48.65) | 0.5750 | 0.9121 | −7.50 (−34.47, 35.45) | 0.8074 | 0.6603 | −20.81 (−46.97, −12.62) | 0.3861 | 0.4710 |
| −                           | 22              | 15.37 (0.95, 42.06) | −3.90 (−30.99, 7.24) | −20.73 (−40.91, −2.75) |
| **Negative inversion of anti-dsDNA antibodies**¹ | | |   | | 29.53 (2.22, 49.15) | 0.5169 | 0.3613 | −11.62 (−33.01, 2.30) | 0.0677 | 0.0604 | −33.41 (−50.78, −20.82) | 0.1116 | 0.3857 |
| −                           | 9               | 11.34 (4.51, 26.96) | 26.42 (−9.20, 96.62) | −15.25 (−34.93, −9.28) |
| **Improvement in low complement level**² |           |            |   |            |              |   |            |
| +                           | 20              | 10.49 (10.10, 43.82) | 0.2413 | 0.1115 | −7.91 (−31.43, 8.36) | 0.6232 | 0.4399 | −25.65 (−38.64, −3.48) | 0.4274 | 0.5091 |
| −                           | 10              | 11.88 (3.54, 18.80) | −5.10 (−31.06, 65.33) | −32.49 (−48.69, −5.69) |

Median (25% quantile–75% quantile)

¹ Negative inversion of anti-dsDNA antibody means anti-dsDNA titre decreased to < 12 IU/ml

² Improvement in low complement level is defined as an increase from baseline in one or more of C3, C4, or CH50

³ P values represent the results of Wilcoxon’s rank-sum test

⁴ Adjusted P-values represent the results of analysis of covariance adjusting for age and BMI

BMI, body mass index; SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index
and the relationship between cytokines and resistin in SLE needs to be thoroughly investigated.

HCQ blocks the processing and assembly of self-peptides into complexes with major histocompatibility complex class II proteins by increasing the pH within intracellular vacuoles [41]. As a result, HCQ interferes with lysosomes and autophagy and inhibits the production of proinflammatory cytokines, including type I interferon, by inhibiting the Toll-like receptor (TLR)7 and TLR9 signaling pathways and the activity of cyclic GMP-AMP synthase [42].

In this study, we found a positive correlation between the HCQ-induced decrease in resistin and a decrease in TNF-α, IL6, IL-8, and IL-1RA. This suggests that the suppression of proinflammatory cytokines by HCQ may decrease serum resistin. However, since serum resistin levels may also be affected by prednisolone and immunosuppressive drugs, which are therapeutic agents that are administered without dose changes, it cannot be ruled out that this decrease in resistin is entirely due to the additional administration of HCQ alone. On the other hand, since no association was found between HCQ-induced changes in adiponectin levels and changes in SLE disease activity in this study, we could not determine that SLE disease activity is related to changes in adiponectin levels. It is also possible that improvement in insulin resistance decreases resistin, as reported for adiponectin in healthy subjects [10, 11]. Ahmed et al. reported that HCQ improves glucose homeostasis in high-fat diet-induced insulin resistance, which is accompanied by a correction in the adipokine imbalance and an alleviation of insulin resistance-induced endothelial dysfunction [43]. Qatanani et al. reported that in transgenic mice expressing human resistin, inflammation of adipose tissue is promoted, lipolysis is enhanced and free fatty acids are accumulated, resulting in increased insulin resistance [44]. This could indicate that a decrease in resistin improved insulin resistance, but the mechanism of how HCQ impacts adipokine levels is not fully understood, and further research is needed.

Persistent disease activity, LN, the presence of antiphospholipid antibodies and glucocorticoid use may be risk factors for CVD in SLE [3, 4], but none were associated with HCQ-induced increases in adiponectin levels in the current study. This indicates that supplemental HCQ improved adipokine levels independent of cardiovascular risk factors and steroid-reducing effects. This effect on adipokines may contribute to the beneficial effects of HCQ on atherosclerosis [7–9] and life expectancy [13, 14].

This study has some limitations. First, we excluded patients whose disease activity was improved by HCQ and in whom the dose of glucocorticoids or immunosuppressants was reduced within 3 months of HCQ administration, which may have resulted in selection bias. Second, we did not monitor adherence by measuring blood HCQ levels. Third, this was a short-term exploratory study with a small sample size and the effect of HCQ administration on atherosclerosis could not be fully verified. Finally, we did not include a control group of healthy subjects or subjects who did not receive HCQ treatment in this study. Larger, long-term prospective observational studies with a control group are needed to confirm the findings of this study. Nevertheless, to the best of our knowledge, this is the first study to show an effect of HCQ on adiponectin and resistin levels in patients with SLE, which we suggest is due to the additional administration of HCQ, since the analysis was performed in a population with no change in treatment other than HCQ during a short time period.
Conclusions

In conclusion, we found that add-on treatment with HCQ modulated serum adipokine levels in patients with SLE. Our results suggest that additional HCQ treatment may improve the serum levels of adipocytokines associated with atherosclerosis.

Supplementary Information  The online version contains supplementary material available at https://doi.org/10.1007/s10067-022-06282-0.

Acknowledgements  We thank Enago (https://www.enago.jp) for editing a draft of this manuscript.

Author contribution  All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. RW and HD planned the study and wrote the manuscript. RW conducted the study and interpreted the results together with KU, SN, HS, TK, NM, MK, TM, KS, MM, RM, and HD. RW and NM conducted statistical analysis of the data obtained in the study. HD and NK reviewed the manuscript for intellectual content. The authors read and approved the final manuscript.

Data availability  The dataset supporting the conclusions of this article is available upon reasonable request.

Declarations

Ethics approval and consent to participate  This study was approved by the ethical committee of Kagawa University (Heisei30-047) and was prospectively registered. All participants gave written informed consent prior to entering the study. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication  Not applicable.

Disclosures  None.

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Author’s comment This manuscript has been published as a preprint at https://www.researchsquare.com/article/rs-942050/v1.