Supplemental Hydroxychloroquine Therapy Regulates Adipokines in Patients With Systemic Lupus Erythematosus With Stable Disease

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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 by SLE disease activity index, Cutaneous Lupus Erythematous Disease Area and Severity Index and Lupus Low Disease Activity State, and serum complement titres, anti-dsDNA antibodies, serum insulin 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 dsDNA antibodies improved lipid levels. HCQ may improve prognosis by controlling disease activity in SLE and reducing risk factors for atherosclerosis.

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 [7–12] and reduces insulin resistance [13, 14] and the risk of thrombosis [15, 16]. It has also been shown to increase survival in patients with SLE [16–18].

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]. However, its mechanism is unclear. 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 prospective study. We enrolled subjects who were diagnosed with SLE using the Systemic Lupus Collaborating Clinics criteria [19] 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 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 [20], 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 [21] and the Lupus Low Disease Activity State criteria [22]. Cutaneous disease activity was evaluated using the Cutaneous Lupus Erythematous Disease Area and Severity Index (CLASI) [23]. 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-1a, 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 mean ± SD, whereas non-parametric distributions were represented as median (interquartile range (IQR) or range). Comparisons between different groups were performed using the Wilcoxon rank sum test. Immunological biomarkers and proinflammatory adipokine levels were compared using the Wilcoxon 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). 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.

Table 1
Characteristics of patients with SLE enrolled in this 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	
SELENA-SLEDAI score, median (range)	4.0 (0–8)
Current skin involvement	24 (59)
CLASI activity score, median, range	2.5, 0–9 (n = 24)
CLASI damage score, median, range	0, 0–5 (n = 24)
Anti-dsDNA positive, no. (%)	15 (37)
Anti-dsDNA, median, range	5.4, 5–82.8

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; NPSLE, neuropsychiatric SLE; LLDAS, Lupus Low Disease Activity State.

Characteristics	N = 41, no. (%)
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 ($\times 10^4$/μl)	20.8, 6.7–32.1
LLDAS	25 (61)
Clinical remission on treatment	4 (10)
Pro-inflammatory cytokines	
TNF-α, pg/ml	3.97 (2.21, 9.13)
IL-6, pg/ml	1.64 (1.23, 4.08)
IL-8, pg/ml	4.65 (1.90, 12.10)
MCP-1, pg/ml	216.47 (151.84, 293.20)
VEGF-A, pg/ml	51.64 (36.50, 80.39)
IL-1RA, pg/ml	674.39 (463.59, 1445.65)
Adipokines	
Adiponectin, μg/ml	8.86 (6.11, 11.72)
Leptin, ng/ml	14.27 (9.07, 27.35)
Resistin, ng/ml	9.11 (6.16, 15.35)
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; NPSLE, neuropsychiatric SLE; LLDAS, Lupus Low Disease Activity State.	

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).

Table 2
Association of adipokine levels with clinical manifestations in patients with SLE at baseline.

Variables		N	Adiponectin (μg/ml)	*P*	Leptin (ng/ml)	*P*	Resistin (ng/ml)	*P*
BMI > 22	+	20	8.71 (4.98, 12.22)	0.9273	24.55 (13.26, 35.21)	0.0055*	9.06 (6.21, 16.11)	0.6669
	−	21	9.16 (6.11, 10.72)		10.86 (8.02, 16.85)		9.26 (5.86, 11.86)	
Glucocorticoids	+	34	9.01 (6.17, 11.59)	0.6154	15.97 (9.95, 30.87)	0.0254*	9.06 (5.96, 14.27)	0.3770
	−	7	7.17 (2.64, 12.13)		7.19 (6.45, 16.61)		10.20 (6.18, 22.08)	
LLDAS or CR	+	29	10.22 (6.24, 12.11)	0.0688	14.25 (9.65, 28.55)	0.6161	9.26 (6.64, 15.35)	0.1561
	−	12	6.61 (4.52, 8.46)		15.73 (6.23, 26.95)		7.15 (4.49, 16.22)	
History of lupus nephritis	+	18	9.78 (5.84, 12.44)	0.2994	21.00 (9.95, 31.91)	0.1599	10.06 (6.23, 16.75)	0.3510
	−	23	7.17 (6.10, 10.70)		14.25 (7.19, 22.63)		8.81 (6.06, 13.51)	
SLEDAI > 4	+	12	7.04 (4.52, 10.24)	0.1827	15.73 (6.23, 26.95)	0.5961	9.50 (4.49, 19.46)	0.5569
	−	29	10.07 (6.14, 12.11)		14.25 (9.65, 28.55)		9.11 (6.22, 14.62)	
Anti-dsDNA positive	+	15	8.86 (6.31, 10.70)	0.7971	13.07 (8.92, 28.26)	0.6357	9.11 (5.50, 13.93)	0.7556

Median (25% quantile, 75% quantile).

*$P < 0.05$, Wilcoxon rank sum test.

BMI, body mass index; SLEDAI, SLE Disease Activity Index; LLDAS, Lupus Low Disease Activity State; CR, Clinical Remission on/without treatment; dsDNA, double-stranded DNA.

Variables		N	Adiponectin (μg/ml)	*P*	Leptin (ng/ml)	*P*	Resistin (ng/ml)	*P*
	−	26	9.04 (4.73, 12.01)		14.56 (9.05, 27.70)		9.14 (6.19, 15.63)	
Low complement	+	20	9.54 (6.46, 14.10)	0.1207	14.34 (6.53, 27.72)	0.3823	9.04 (4.89, 13.30)	0.2353
	−	21	8.75 (4.01, 10.54)		14.27 (9.83, 29.83)		9.11 (7.20, 17.14	
Median (25% quantile, 75% quantile).								
*$P < 0.05$, Wilcoxon rank sum test.								
BMI, body mass index; SLEDAI, SLE Disease Activity Index; LLDAS, Lupus Low Disease Activity State; CR, Clinical Remission on/without treatment; dsDNA, double-stranded DNA.								

Adiponectin levels were negatively correlated with complement factors C3 and C4 (r = − 0.33, $P = 0.0357$ and r = − 0.39, $P = 0.01116$, respectively), whereas leptin was positively correlated with C3 and CH50 levels (r = − 0.33, $P = 0.0357$ and r = − 0.39, $P = 0.0116$, respectively). There was no significant relationship between SLEDAI and dsDNA antibodies and serum adipokine levels. These results are shown in Table 2 and Additional file 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).

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 change in leptin level was negatively correlated with a decrease in anti-dsDNA antibodies (Additional file 2).

There was also no significant association between changes in adipokine levels and the SLEDAI score, skin involvement or renal involvement (Table 3, Additional file 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 (Additional file 3).

Table 3
Association between clinical parameters and changes in adipokine levels.

Rate of change in cytokines¶		N	Adiponectin, %	*P*	Leptin, %	*P*	Resistin, %	*P*
BMI > 22	+	20	17.83 (7.61, 52.76)	0.4113	−4.22 (− 28.21, 8.19)	0.7764	−16.97 (− 39.42, − 4.02)	0.4407
	−	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	−7.50 (− 30.45, 9.53)	0.8868	−20.00 (− 43.60, − 3.35)	0.1651
	−	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	−2.15 (− 29.15, 11.98)	0.6815	−30.57 (− 49.96, − 14.65)	0.0951
	−	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	−7.50 (− 34.47, 35.45)	0.8074	−20.81 (− 46.97, − 12.62)	0.3861
	−	22	15.37 (0.95, 42.06)		−3.90 (− 30.99, 7.24)		−20.73 (− 40.91, − 2.75)	

¶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.

**P* < 0.05, Wilcoxon rank sum test.

Rate of change in cytokines¶		N	Adiponectin, %	*P*	Leptin, %	*P*	Resistin, %	*P*
Negative inversion of anti-dsDNA antibodies*[1]	+	6	29.53 (2.22, 49.15)	0.5169	−11.62 (− 33.01, 2.30)	0.0677	−33.41 (− 50.78, − 20.82)	0.1116
	−	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]	+	10	20.49 (10.10, 43.82)	0.2413	−7.91 (− 31.43, 8.36)	0.6232	−25.65 (− 38.64, − 3.48)	0.4274
	−	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.

**P* < 0.05, Wilcoxon rank sum test.

Among the adipokines, the change in serum resistin level after HCQ was correlated with a significant reduction in serum TNF-α, IL-6, IL-8, and IL-1RA levels (Table 4). However, the increase in adiponectin and leptin levels was not correlated with a change in the levels of these cytokines (Table 4).

Table 4
Association between changes in pro-inflammatory cytokines and changes in adipokine levels.

Cytokine	Adiponectin (μg/ml)		Leptin (ng/ml)		Resistin (ng/ml)	
	r	*P*	r	*P*	r	*P*
TNF-α	−0.1405	0.4209	−0.3456	0.0453	0.3887	0.0231*
IL-6	−0.1284	0.4237	−0.1285	0.4295	0.3810	0.0153*
IL-8	−0.1586	0.3415	−0.2542	0.1289	0.5438	0.0005*
MCP-1	0.0483	0.7642	−0.0090	0.9558	0.2061	0.2021
VEGF-A	−0.2585	0.1172	−0.2568	0.1250	0.2844	0.0880
IL-1RA	−0.0602	0.7086	−0.0840	0.6064	0.8893	< 0.0001*

The correlation between the rate of changes in pro-inflammatory cytokines and the rate of changes in adipokine levels was analysed using univariate analysis.

*Data were considered significant at $P < 0.05$.

Pearson's correlation coefficient (r) was used to compute the correlations between variables.

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 [13]. HCQ significantly increased adiponectin levels, indicating a possible anti-inflammatory effect in adipose tissue. Adiponectin has been shown to influence insulin sensitivity [24–26], and the mechanism by which HCQ affects insulin sensitivity is thought to be via the modulation of adipose tissue inflammation and adiponectin production [27–29].

In patients with SLE, increased serum adiponectin, leptin and resistin levels have been reported compared with healthy subjects [30–34], but several reports showed no difference. Therefore, there is no consensus on whether adipokines are elevated in SLE [35–39]. 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 [30, 31, 33, 40, 41]. 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 preexisting 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 [33, 35]. Additionally, serum leptin levels were negatively correlated with disease activity and anti-dsDNA antibodies and positively correlated with hypocomplementemia [35]. 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 [30, 33].

Resistin is an inflammatory regulator that acts downstream of inflammation [42, 43]. 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 [44–48], which promotes an inflammatory response. However, several endogenous substances, such as proinflammatory cytokines, also upregulate resistin expression [42, 45, 46, 48]. 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 [49, 50]. In SLE, a correlation between serum resistin level and serum TNF-α and IL-6 levels has been

demonstrated [39, 51], but reports are scarce 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 [52]. 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 [53, 54].

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 no association was found between HCQ-induced changes in adipokine levels and changes in SLE disease activity in this study, we could not determine that SLE disease activity is related to changes in adipokine levels. It is also possible that improvement in insulin resistance decreases resistin, as reported for adiponectin in healthy subjects [13, 14]. 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 [55]. 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 [56]. 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 [7–11] and life expectancy [16–18].

This study has some limitations. First, we excluded patients whose disease activity was improved by HCQ by excluding patients from the analysis who had reduced their glucocorticoid dose 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, the sample size was small. Finally, we did not include a healthy control group in this study. Nevertheless, our study has the advantage that, to the best of our knowledge, it is the first to show an effect of HCQ on adiponectin and resistin levels in patients with SLE.

Conclusions

In conclusion, we found that add-on treatment with HCQ modulated serum adipokine levels in patients with SLE. Our results suggest that supplemental treatment with HCQ may improve atherosclerosis by modulating adipokines in patients with SLE and improve their prognosis.

Abbreviations

systemic lupus erythematosus; SLE, Hydroxychloroquine; HCQ, interleukin; IL, cardiovascular disease; CVD, lupus nephritis; LN, systemic lupus erythematosus disease activity index; SLEDAI, body mass index; BMI, Cutaneous Lupus Erythematous Disease Area and Severity Index; CLASI, anti-double stranded DNA; dsDNA, interquartile range; IQR, Toll-like receptor; TLR

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.

Availability of data and materials

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

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

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, MK, TM, KS, MM, RM, and HD. MMFM and NK reviewed the manuscript for intellectual content. The authors read and approved the final manuscript.

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Figures

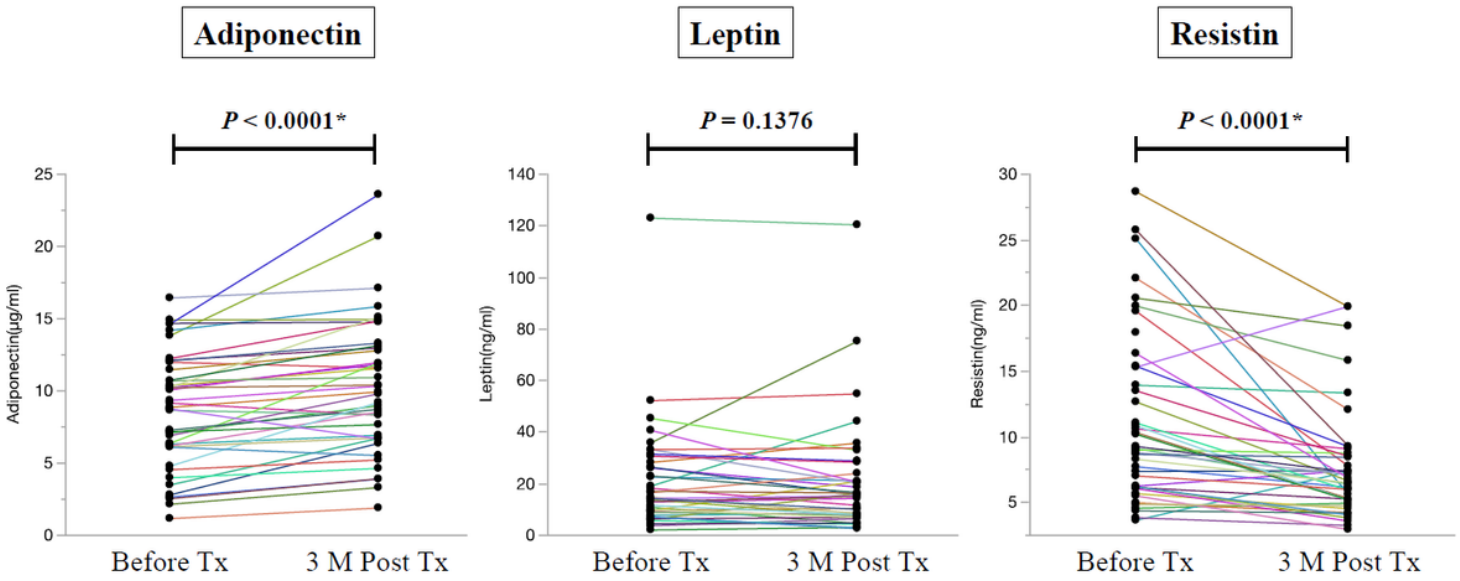

Figure 1

Serum adipokine levels before and after hydroxychloroquine treatment. Serum levels of the indicated adipokines and factors were measured before or after 3 months (3M Post) treatment (Tx) with hydroxychloroquine. Colored lines represent individual patients. NS: not significant. * indicates a P-value of less than 0.05. P-values were determined by the Wilcoxon signed-rank test.

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