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Serum Adipokine Levels and Associations with Patient-Reported Fatigue in Systemic Lupus Erythematosus

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Abstract

Background—Physical activity ameliorates fatigue in systemic lupus erythematosus (SLE) patients by an unknown mechanism. Adipokines, which are influenced by adiposity and physical activity, may be associated with patient-reported fatigue.

Objective—We describe cross-sectional associations between adipokines and fatigue, physical activity, and SLE disease activity.

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Disclosure Statement

None of the authors have conflicts of interest to disclose.

Methods—We measured adipokines, self-reported fatigue, and objective physical activity in 129 SLE patients. Fatigue was assessed with the Fatigue Severity Scale (FSS) and Patient Reported Outcomes Measurement Information System® (PROMIS®) Fatigue score. Disease activity was measured with the Safety of Estrogens in Systemic Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). Participants wore an accelerometer for 7 days to measure physical activity. Leptin, adiponectin, and resistin were measured in stored serum with a Luminex bead-based assay. Multivariable regression models assessed relationships between fatigue and adipokines, and Spearman correlation coefficients summarized associations between adipokines, physical activity, and SELENA-SLEDAI.

Results—Median adipokine levels were: leptin 30.5 ng/ml (Interquartile Range 14.0, 56.6), adiponectin 11.6 µg/ml (7.2, 16.8) and resistin 1.4 ng/ml (1.0, 2.2). Associations between adipokines and FSS or PROMIS Fatigue were not significant. Body mass index (BMI) 30 kg/m² was associated with FSS and PROMIS Fatigue in regression analyses (p<0.05). Weak correlations between leptin, adiponectin, leptin/adiponectin (L/A) ratio, and physical activity and between adiponectin and SELENA-SLEDAI score were not significant after adjusting for BMI.

Conclusion—Adipokines were not associated with fatigue in SLE. Adipokines were correlated with physical activity (leptin, adiponectin, L/A ratio) and SLE disease activity (adiponectin), but most of these associations were explained by BMI.

Keywords

Systemic lupus erythematosus; adipokines; fatigue; physical activity

INTRODUCTION

Fatigue is an almost universal symptom of systemic lupus erythematosus (SLE), a chronic autoimmune disease with heterogeneous manifestations [1]. Up to 90% of patients report some degree of fatigue [2,3], and half identify fatigue as their most disabling SLE symptom [4]. Fatigued SLE patients have higher direct and indirect health care costs than non-fatigued patients [5]. Addressing patient-reported fatigue is therefore a critical part of caring for the SLE patient, although evidence-based treatment options are limited [6]. Aerobic exercise is known to ameliorate fatigue in SLE patients [7]. We have shown that increased time spent in moderate-vigorous physical activity, objectively measured with accelerometers, is correlated with less patient-reported fatigue [8]. However, the mechanism by which physical activity mitigates fatigue is unknown but has implications for development of more targeted fatigue therapy.

Changes in adiposity and circulating adipokines, cytokines produced by adipose tissue, are a potential link between physical activity and SLE-related fatigue. Leptin, adiponectin, and resistin are adipokines that have well-characterized immune-modulatory roles and have been implicated in the pathogenesis of autoimmune disease, including SLE [9–11]. Leptin, which induces satiety, increases with higher body mass index (BMI) and may decrease with prolonged exercise [12]. It is a pro-inflammatory adipokine [9,10], and some studies have reported higher leptin levels in SLE patients with more active disease [13,14]. In contrast, adiponectin is an anti-inflammatory adipokine that enhances insulin sensitivity. Serum levels

of adiponectin are inversely related to BMI [9,10] and may increase with exercise [12]. Adiponectin tends to be higher in SLE patients than healthy controls [15–18], and higher levels correlate with lupus nephritis [11]. Finally, resistin levels increase with higher BMI [9,10], and, in one study of post-menopausal women, levels decreased following resistance training [19]. Resistin is pro-inflammatory, and higher levels are associated with laboratory markers of increased SLE activity, such as sedimentation rate [20] and proteinuria [21], but not with SLE disease activity indices [16,13,17,22].

Leptin, adiponectin, and resistin have been evaluated for associations with fatigue in other chronic disease populations, but never in SLE. Higher circulating leptin is correlated with more severe fatigue in patients with chronic hepatitis C [23,24], irritable bowel syndrome [25], and chronic fatigue syndrome [26]. One study of fibromyalgia patients found that low levels of adiponectin in the cerebrospinal fluid (CSF) correlated with greater patient-reported fatigue [27]. In this same study, higher resistin levels in serum and CSF correlated with less fatigue at baseline and after an exercise program.

The primary aim of this study was to evaluate cross-sectional relationships between serum adipokine concentrations and subjective fatigue in SLE patients. We hypothesized that higher leptin, resistin, and leptin/adiponectin (L/A) ratio and lower adiponectin would be associated with higher levels of patient-reported fatigue. Secondary study aims were to evaluate associations between adipokines, physical activity, and SLE disease activity. We expected that less time spent in physical activity would correlate with higher leptin and resistin, lower adiponectin, and higher L/A ratio. Finally, we expected higher SLE disease activity to be associated with higher leptin, adiponectin, and resistin levels but lower L/A ratio.

MATERIALS AND METHODS

This investigation is ancillary to Activity in Lupus to Energize and Renew (ALTER), a cross-sectional study in SLE patients designed to test the hypothesis that higher levels of subjective fatigue are associated with less time spent in physical activity objectively measured with an accelerometer. The Institutional Review Board at Northwestern University approved the study protocol and participants provided informed consent prior to enrollment according to the Declaration of Helsinki. Detailed study methods have been published elsewhere [28,8]. Briefly, participants were recruited consecutively from the Chicago Lupus Database, an ongoing registry of patients 18 years of age who meet at least 4 of the 1982 or updated 1997 American College of Rheumatology criteria for SLE [29,30]. One hundred thirty participants initially enrolled in ALTER, but one participant was excluded when review of a skin biopsy did not confirm malar or discoid lesions. Characteristics of the remaining 129 ALTER participants compared to the remaining members of the Chicago Lupus Database have been previously reported [28].

Data Collection

ALTER study visits consisted of demographic data collection, measurement of height and weight by trained research personnel, completion of patient-reported outcome measures, and instruction on the use of accelerometers for physical activity monitoring. BMI was

calculated from height and weight. Each participant was interviewed and examined by a trained physician to measure SLE disease activity and damage. Disease activity was assessed with the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). SELENA-SLEDAI scores range from 0 to 105, with a score <4 indicating inactive disease [31]. SLE disease damage was measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), which has a maximum score of 46 [32]. Blood samples were collected, processed according to laboratory standards, and serum stored at -80°C .

Adipokine Measurement

Serum adipokines were measured with a Luminex bead-based assay per the manufacturer's instructions (eBioscience, San Diego, CA). Lower limits of detection for leptin, adiponectin, and resistin assays were 19.31 pg/ml, 56.15 pg/ml, and 5.74 pg/ml, respectively.

Patient-Reported Outcome Measures

The primary fatigue outcome was the Fatigue Severity Scale (FSS), a commonly used tool for measuring fatigue in SLE patients [33]. This 9-item questionnaire assesses the impact of fatigue on patient functioning during the preceding 2 weeks. Scores range from 0 to 7 with higher scores indicating worse fatigue. A score ≥ 4 is considered a clinically relevant level of fatigue [33].

Patient Reported Outcomes Measurement Information System[®] (PROMIS[®]) instruments were secondarily used to assess fatigue and sleep. PROMIS scores are reported using a T-score metric, which rescales a raw score into a standardized score with a mean of 50 and a standard deviation (SD) of 10. A score of 50 represents the average for the general U.S. population. Participants completed Version 1.0 (8a) PROMIS 8-item short forms for Fatigue and Sleep Disturbance using a 5-item response scale.

PROMIS Fatigue evaluates fatigue frequency, intensity, duration, and impact on an individual's daily functioning during the preceding 7 days. PROMIS Sleep Disturbance measures sleep quality and restfulness [34]. The higher the PROMIS T-score, the more of that domain (e.g., fatigue) the patient experiences. Thus, higher fatigue and sleep disturbance scores indicate worse health status in these domains. We have previously reported the internal consistency of these PROMIS instruments, as well as a strong correlation between FSS and PROMIS Fatigue scores in this SLE sample [8].

Physical Activity Measurement

Participants were provided with a GT3X ActiGraph triaxial accelerometer (ActiGraph; Pensacola, FL) and instructed to wear it over the right hip during waking hours for 7 consecutive days, as previously described [28,8]. Accelerometers were returned to the research center and data analyzed using the manufacturer's software. The GT3X accelerometer measures acceleration in the vertical, antero-posterior, and medio-lateral axes. Triaxial vector magnitude (VM) was calculated for each minute as the VM of the three uniaxial counts [35]. Average daily VM accelerometer counts were determined as a measure

of total physical activity (combined light, moderate, and vigorous intensity activities) performed during the monitoring period. Using algorithms developed by Choi and colleagues, a valid day of monitoring was based on evidence of ≥ 10 hours of accelerometer wear time after identifying periods of non-wear [36,37]. Analyses incorporating a physical activity assessment were limited to persons with ≥ 4 valid days of monitoring to provide reliable physical activity estimates.

Statistical Analysis

Results from our study are summarized using means (SD) and medians (interquartile range [IQR]) for continuous variables and frequencies and percentages for categorical variables. Adipokine concentrations were logarithmically transformed (natural log scale) to obtain more normally distributed variables for statistical analysis; the leptin/adiponectin ratio (L/A ratio) was calculated and similarly analyzed. Linear regression models were used to analyze relationships between fatigue (FSS or PROMIS Fatigue; outcome variables) and each adipokine (leptin, adiponectin, L/A ratio, or resistin; predictor variable [log scale]). Models were unadjusted, and then sequentially adjusted for age, sex, and race/ethnicity, and also BMI, and other covariables: SELENA-SLEDAI score, average daily VM accelerometer counts and accelerometer wear time, and PROMIS Sleep Disturbance T-score. Logistic regression models were also used to analyze relationships between fatigue, categorized as high fatigue versus low (FSS ≥ 4 was defined as high), and adipokine concentrations. Reference ranges have not been established for PROMIS Fatigue in SLE patients, so a score ≥ 60, i.e., one standard deviation above the general population mean, was used to define high fatigue for this measure. Logistic regression models were developed using the same covariables and modeling strategy as in the linear regression models. Finally, Spearman correlation coefficients (r) were used to summarize associations (unadjusted and adjusted) between adipokines (log scale) and BMI, SELENA-SLEDAI score, and physical activity (average daily VM accelerometer counts), as well as between fatigue (FSS and PROMIS Fatigue) and BMI.

RESULTS

Characteristics of the study sample are shown in Table 1. Participants were predominantly female and Caucasian. Average BMI was 28.1 kg/m² (SD 8.2), and 24.0% and 31.8% of participants met BMI cutoffs for being overweight (BMI 25.0–29.9 kg/m²) or obese (BMI ≥ 30 kg/m²), respectively. SELENA-SLEDAI and SDI scores were consistent with low disease activity and damage.

Among the patient-reported outcome measures (Table 1), average FSS scores were consistent with a clinically meaningful level of fatigue. Similarly, PROMIS Fatigue and Sleep Disturbance scores were consistent with worse health status in each domain compared to the general U.S. population. Higher BMI weakly correlated with increased fatigue measured with both FSS (r=0.19, p=0.03) and PROMIS Fatigue (r=0.20, p=0.03).

One hundred twenty three participants had ≥ 4 valid days of accelerometer data available for analysis, and 109 (88.6%) of these had at least six valid days of monitoring. Accelerometers were worn for 14.4 hours/day (SD 1.3) on average (Table 1). Mean daily VM accelerometer

counts, reflecting average daily time spent in total physical activity, was similar to that described in a healthy population, as reported previously [28].

Mean and median concentrations of leptin, adiponectin, L/A ratio, and resistin are shown in Table 2, overall and stratified by BMI. Median leptin levels (log scale) and L/A ratio were significantly higher in overweight and obese patients compared to those with normal BMI. Obese patients had lower adiponectin levels on average (log scale) than patients with normal or overweight BMI. In the full sample, higher BMI correlated with higher leptin ($r=0.80$, $p<0.001$), lower adiponectin ($r=-0.35$, $p<0.001$), and higher L/A ratio ($r=0.77$, $p<0.001$). No significant correlations between resistin and BMI were found across BMI strata. Among patients taking prednisone, resistin levels (log scale) were higher in obese participants taking ($n=20$) versus not taking ($n=20$) prednisone ($p = 0.02$). No other significant difference in adipokine levels was found among participants with prednisone use.

Adipokines and Fatigue

Results of linear regression models evaluating relationships between adipokines (log scale) and fatigue are shown in Table 3. Leptin, adiponectin, and resistin were not significantly associated with FSS or PROMIS Fatigue in unadjusted or any adjusted models. L/A ratio was not significantly associated with FSS, and only significantly associated with PROMIS Fatigue score in the model adjusted for age, sex, and race/ethnicity. However, this relationship was no longer significant after adjusting for BMI. Further, obesity (BMI ≥ 30 kg/m²) was significantly associated with both FSS and PROMIS Fatigue in all adjusted regression analyses ($p<0.05$), except in a model evaluating the relationship between adiponectin and FSS adjusted for average daily VM accelerometer counts and accelerometer wear time (data not shown). No independent associations between adipokines and fatigue (FSS or PROMIS) were found in linear regression analyses stratified by BMI (<25 kg/m² versus 25.0–29.9 kg/m² versus ≥ 30 kg/m²).

In logistic regression analyses, leptin was associated with both FSS (odds ratio [OR] 1.46, 95% confidence interval [1.01; 2.13]) and PROMIS Fatigue (OR 1.53, [1.03, 2.26]) in unadjusted models only. These relationships were no longer significant after adjusting for age, sex, and race/ethnicity (FSS OR 1.42, [0.93, 2.170]; PROMIS Fatigue OR 1.49, [0.95, 2.33]), BMI (FSS OR 0.95, [0.51, 1.76]; PROMIS Fatigue OR 0.94, [0.49, 1.79]), or accelerometer counts and wear time (FSS OR 0.94, [0.49, 1.78]; PROMIS Fatigue OR 0.88, [0.46, 1.70]). There were no significant associations between either categorical fatigue measure and adiponectin, L/A ratio, or resistin in unadjusted or adjusted models.

Adipokines and Physical Activity

Higher leptin, lower adiponectin, and higher L/A ratio were weakly associated with less time spent in physical activity (Table 4). However, these correlations were no longer significant after adjusting for BMI. No significant associations were found between resistin and physical activity.

Adipokines and SLE Disease Activity

Higher adiponectin was weakly correlated with higher SELENA-SLEDAI score, but this was not significant after adjusting for BMI (Table 4). No significant correlations were found between SELENA-SLEDAI and leptin, L/A ratio, or resistin.

DISCUSSION

This is the first study to evaluate relationships between serum adipokines and fatigue in patients with SLE. Leptin, adiponectin, and resistin were not independently associated with patient-reported fatigue in unadjusted (univariate) and adjusted (multivariable) linear regression models. However, BMI significantly but weakly correlated with FSS and PROMIS Fatigue, and obesity (BMI ≥ 30 kg/m²) was independently associated with both fatigue measures. Leptin was associated with both fatigue measures in unadjusted analyses, but these relationships were no longer significant after adjusting for age, sex, and race/ethnicity. Adipokine levels significantly correlated with physical activity (leptin, adiponectin, and L/A ratio) and SLE disease activity (adiponectin), but these associations were not evident after adjusting for BMI. Our results suggest that BMI more strongly influences patient-reported fatigue than leptin, adiponectin, or resistin in our modest cross-sectional pilot study of individuals with SLE who had low disease activity and damage at the time of study.

Others have evaluated the influence of adipokines on fatigue in chronic diseases [23,25–27,24]. Interest in the relationship between leptin and fatigue stems from animal studies implicating leptin as a neuroendocrine mediator of sickness behavior [38,39]. Piche and colleagues reported an independent association between serum leptin levels and fatigue (Fatigue Impact Scale) in a cross-sectional study of 51 patients with irritable bowel syndrome [25]. Leptin was significantly correlated with fatigue even after adjusting for BMI, and only leptin was independently associated with fatigue in multivariable analyses adjusting for age, sex, fat mass and BMI. In a small longitudinal study of patients with chronic fatigue syndrome (n=10), Stringer and colleagues found that daily fluctuations in self-reported fatigue (Visual Analog Scale) significantly correlated with leptin levels, although adjustment for BMI was not included in statistical analyses [26]. Others have also demonstrated relationships between leptin and fatigue in patients with chronic hepatitis C infection [23,24], although the influence of BMI was not rigorously evaluated.

Only one study has directly evaluated associations between adiponectin, resistin, and fatigue [27]. In that cohort of 48 fibromyalgia patients, lower levels of adiponectin in the CSF correlated with higher cross-sectional fatigue (Multidimensional Fatigue Inventory). Further, baseline and change in resistin after a 15 week walking program correlated with baseline and change in fatigue; this relationship was strongest in obese patients.

There are several possibilities for why only obesity was significantly associated with patient-reported fatigue in our study. The cross-sectional study design did not allow us to evaluate dynamic changes in adipokine concentrations or fatigue, and important relationships may be detected if evaluated longitudinally. Further, although patient-reported fatigue was clinically significant in our SLE patients, the degree of fatigue was relatively mild on average.

Adipokine associations with fatigue may be more apparent in patients with higher FSS or PROMIS Fatigue scores. Finally, obesity has been associated with increased fatigue in SLE patients [40,41], and increased BMI significantly correlated with higher scores for both fatigue measures in our sample. BMI may directly or indirectly influence fatigue through alternative mechanisms that are independent of circulating adipokines. Our results together with these other studies provide rationale for continuing to examine associations between adipokines and fatigue in chronic disease, but also underscore the need to evaluate this relationship longitudinally and in the context of adiposity and BMI.

This is also the first study to evaluate relationships between adipokines and physical activity in patients with SLE. In our cross-sectional study, more time spent in physical activity was associated with lower leptin, higher adiponectin, and a lower L/A ratio. These associations were expected based on longitudinal studies evaluating the influence of aerobic exercise on leptin and adiponectin in healthy and overweight or obese individuals [12,42–47]. For example, Gondim and colleagues assessed adipokines at baseline and throughout a supervised exercise program that consisted of either swimming and/or water aerobics twice weekly [46]. After 12 months, leptin levels were decreased compared to baseline in overweight and obese participants, and this decrease was independent of weight loss. In contrast, adiponectin levels have generally been shown to increase in overweight or obese individuals following 12–24 weeks of aerobic exercise, such as walking [43,44,48], and one study found this increase to be independent of changes of body composition [45]. Leptin and adiponectin may also acutely decrease and increase, respectively, during endurance exercise (cycling) in healthy individuals [47]. Longitudinal studies on the influence of physical activity on resistin levels have been conflicting [46,48,19], and we did not find a significant association in our SLE patients.

BMI in our SLE patients was consistent with an overweight population on average. The associations between leptin, adiponectin, and L/A ratio and physical activity were no longer significant after adjusting for BMI, suggesting that BMI had a stronger influence on adipokine levels than cross-sectionally assessed physical activity. Differences in the type and intensity of routine physical activity performed on average by our SLE patients compared to the structured exercise programs implemented in other studies may have attenuated these associations after accounting for BMI.

Mean levels of leptin and adiponectin in our patients were similar to those reported in other SLE cohorts [14,13,16,15,18,17,49], but mean resistin level in our SLE sample was lower [13,16,17,20]. Leptin was not correlated with SLE disease activity, and an association between higher leptin and increased SLE disease activity has been inconsistently reported in the literature [13,14,16,17,49]. The observed weak positive correlation between adiponectin and SLE disease activity was no longer significant after adjusting for BMI, suggesting that adiposity likely mediated this association. This result is consistent with other SLE studies, as adiponectin has not previously been associated with general SLE disease activity [16,13,14,17,49]. Similar to our results, no significant associations between resistin and SLE disease activity have been reported [16,13,20,17].

There are several limitations to our study. As an ancillary investigation to the parent study ALTER, the sample size was fixed and not specifically powered to evaluate associations between adipokines and fatigue, physical activity, or SLE disease activity. Additionally, the amount of time spent in physical activity was relatively low, and SELENA-SLEDAI scores were consistent with inactive disease on average. Adipokine associations with physical activity and SLE disease activity may be more apparent in more physically active patients and those with higher SELENA-SLEDAI scores, respectively. Leptin and adiponectin levels are influenced by sleep patterns [50]. We did not collect specific details on participants' sleep, but linear regression results were similar after adjusting for patient-reported sleep disturbance. We were also unable to fully assess the relationship between hydroxychloroquine or immunosuppressant use on adipokine levels due our small sample size. Prednisone did not appear to significantly influence adipokine levels in normal or overweight individuals, and was only associated with resistin levels in obese participants. Finally, the laboratory testing was completed on stored serum. Adipokine degradation is possible despite serum collection and storage per laboratory standards.

In conclusion, leptin, adiponectin, L/A ratio, and resistin were not independently associated with patient-reported fatigue in this pilot study of SLE patients. Obesity was associated with both FSS and PROMIS Fatigue scores. Expected significant correlations were found between leptin, adiponectin, and L/A ratio and physical activity, as well as between adiponectin and SLE disease activity, but these associations were explained by BMI. Future studies should evaluate adipokines and fatigue in a larger SLE sample and prospectively assess longitudinal relationships between serum adipokines and SLE-related fatigue.

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Table 1

Descriptive characteristics (n=129).

Characteristics	N (%)	Mean $\pm$ SD
Women	121 (93.8)	
Caucasian race/ethnicity	69 (53.5)	
Age (years)		45.5 $\pm$ 10.9
BMI (kg/m ²)		28.1 $\pm$ 8.2
Weight		
Normal (BMI <25 kg/m ²)	57 (44.2)	
Overweight (BMI 25.0–29.9 kg/m ²)	31 (24.0)	
Obese (BMI $\geq$ 30 kg/m ²)	41 (31.8)	
SELENA-SLEDAI score		2.4 $\pm$ 2.8
SDI score		1.7 $\pm$ 2.2
Current medication use ^a		
Hydroxychloroquine	109 (85.2)	
Corticosteroids	60 (46.9)	
Prednisone dose (mg) (n=60)		9.8 $\pm$ 10.4
Immunosuppressant	54 (42.2)	
Mycophenolate mofetil	23 (18.0)	
Azathioprine	14 (10.9)	
Methotrexate	14 (10.9)	
Cyclosporine	1 (0.8)	
Leflunomide	1 (0.8)	
Tacrolimus	1 (0.8)	
Patient-reported outcomes		
Fatigue Severity Scale (FSS)		4.4 $\pm$ 1.6
PROMIS Fatigue ^b		56.2 $\pm$ 9.8
PROMIS Sleep Disturbance		56.1 $\pm$ 10.3
Physical activity measurements ^c		
Accelerometer wear time (hr/day)		14.4 $\pm$ 1.3
Accelerometer counts ^d		490225.6 $\pm$ 192874.3

Continuous variables are summarized as mean $\pm$ standard deviation (SD) and categorical variables as number (%) of patients. BMI indicates body mass index; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; SDI, SLICC/ACR (Systemic Lupus International Collaborative Clinics/American College of Rheumatology) Damage Index; PROMIS, Patient Reported Outcomes Measurement Information System.

^a n=128 participants with medication data

^b PROMIS measures are scored using a T-score metric, mean=50, SD=10 referenced to the U.S. general population.

^c n=123 participants with $\geq$ 4 valid days of accelerometer wear.

^d Average daily vector magnitude accelerometer counts.

Table 2

Serum adipokine concentrations, overall and stratified by BMI

Adipokine	Summary Statistic	Full Sample (n=129)	BMI		
			<25 kg/m ² (n=57)	25.0–29.9 kg/m ² (n=31)	30 kg/m ² (n=41)
Leptin (ng/ml)	Mean	44.2	16.4	41.3	85.1
	Median (IQR)	30.5 (14.0, 56.5)	12.9 (3.1, 51.5)	36.4 (9.7, 164.8) ^a	61.4 (21.8, 321.6) ^b
Adiponectin (µg/ml)	Mean (SD)	13.5	14.5	16.4	9.9
	Median (IQR)	11.6 (7.2, 16.8)	14.0 (2.5, 37.0)	12.9 (4.7, 97.2)	7.8 (1.2, 55.1) ^c
L/A ratio	Mean (SD)	5.9	1.6	4.1	13.2
	Median (IQR)	2.5 (1.0, 6.6)	1.0 (0.2, 7.9)	2.6 (0.4, 25.5) ^a	9.7 (1.5, 95.0) ^b
Resistin (ng/ml)	Mean (SD)	1.9	1.8	2.1	1.9
	Median (IQR)	1.4 (1.0, 2.2)	1.3 (0.4, 9.8)	1.7 (0.4, 7.7)	1.5 (0.5, 5.6)

BMI indicates body mass index; SD, standard deviation; IQR, interquartile range; L/A ratio, leptin/adiponectin ratio.

Adipokine concentrations were logarithmically transformed (natural log) to compare summary values between BMI strata:

^a p< 0.001 compared to BMI <25 kg/m²^b p< 0.001 compared to BMI <25 kg/m² and BMI 25.0–29.9 kg/m²^c p< 0.01 compared to BMI <25 kg/m² and BMI 25.0–29.9 kg/m²

Table 3

Coefficients (p-values) for each serum adipokine concentration (predictor variable, log scale) and each fatigue measure (outcome variable) in the unadjusted and multivariable regression models (n=129).

Model	Regression Coefficient	Fatigue Severity Scale (FSS)				PROMIS Fatigue			
		Leptin	Adiponectin	L/A ratio	Resistin	Leptin	Adiponectin	L/A ratio	Resistin
Unadjusted	β	0.25	-0.11	0.17	0.36	1.60	-1.12	1.20	1.91
	p-value	0.10	0.63	0.14	0.11	0.072	0.39	0.072	0.16
Model 1	β	0.26	-0.15	0.20	0.35	1.90	-1.62	1.65	1.91
	p-value	0.13	0.53	0.12	0.12	0.058	0.25	0.033	0.16
Model 2	β	-0.12	0.080	-0.11	0.32	-0.066	-0.38	0.17	1.70
	p-value	0.61	0.74	0.53	0.15	0.96	0.79	0.87	0.21

Adipokine concentrations were logarithmically transformed (natural log) for statistical analysis. Regression coefficients represent the expected change in fatigue (FSS or PROMIS) per unit change in the log adipokine concentration after adjusting for the other predictors. Significant associations are bolded. PROMIS indicates Patient Reported Outcomes Measurement Information System; L/A ratio, leptin/adiponectin ratio.

Model 1: Adjusted for age, sex, and race/ethnicity

Model 2: Adjusted for age, sex, race/ethnicity, and BMI

Table 4

Spearman correlation coefficients for adipokines versus physical activity and SLE disease activity.

	Accelerometer counts ^a r (p-value) n=123		SELENA-SLEDAI r (p-value) n=129	
	Unadjusted	Adjusted for BMI	Unadjusted	Adjusted for BMI
Leptin	−0.25 (0.005)	−0.063 (0.49)	0.021 (0.82)	0.16 (0.07)
Adiponectin	0.20 (0.031)	0.11 (0.25)	0.18 (0.043)	0.15 (0.09)
L/A ratio	−0.27 (0.003)	−0.092 (0.32)	−0.072 (0.42)	0.011 (0.91)
Resistin	−0.074 (0.42)	−0.043 (0.64)	0.080 (0.37)	0.094 (0.30)

Adipokine concentrations were logarithmically transformed (natural log) for statistical analysis. Significant associations are bolded. SLE indicates systemic lupus erythematosus; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index; BMI, body mass index; L/A ratio, leptin/adiponectin ratio.

^a Average daily vector magnitude accelerometer counts. Analyses adjusted for accelerometer wear time and exclude six participants with 4 valid days of monitoring.