Association of alcohol consumption and fatigue in SLE: a cross-sectional study from Lupus Registry of Nationwide Institution (LUNA) cohort

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Abstract

Objective: Fatigue is one of the most common complaints and is a potentially modifiable issue in systemic lupus erythematosus (SLE). Studies suggest that alcohol consumption has a protective effect against the development of SLE; however, an association between alcohol consumption and fatigue in patients with SLE has not been studied. Here we assessed whether alcohol consumption was associated with fatigue using lupus patient-reported outcomes (LupusPRO).

Methods: This cross-sectional study, conducted between 2018 and 2019, included 534 patients (median age, 45 years; 87.3% female) from 10 institutions in Japan. The main exposure was alcohol consumption, which was defined as the frequency of drinking [<1 day/month (none group), ≤1 day/week (moderate group), and ≥2 days/week (frequent group)]. The outcome measure was the Pain Vitality domain score in LupusPRO. Multiple regression analysis was performed as the primary analysis after adjusting for confounding factors, such as age, sex, and damage. Subsequently, the same analysis was performed as a sensitivity analysis after multiple imputations (MIs) for missing data (n=580).

Results: In total, 326 (61.0%) patients were categorized into the none group, 121 (22.7%) into the moderate group, and 87 (16.3%) into the frequent group. The frequent group was independently associated with less fatigue compared with none group [β = 5.98 (95% CI 0.19 to 11.76), P = 0.04], and the results did not substantially deviate after MI.

Conclusions: Frequent drinking was associated with less fatigue, which highlights the need for further longitudinal studies focusing on drinking habits in patients with SLE.

Introduction

Systemic lupus erythematosus (SLE) is a systemic chronic autoimmune disease that presents with various symptoms. Owing to recent progress in the therapeutic approaches, long-term prognosis and management of organ damage have been improving; however, improving the health-related quality of life (HRQOL) remains one of the most challenging problems. Fatigue, which is a sub-concept of HRQOL, is one of the most common complaints in patients with SLE. Chronic diseases similar to SLE, such as hemodialysis, diabetes mellitus, and fatigue, are known to be associated with cardiovascular events and mortality [1-4]. In previous studies, fatigue was reported by 67-90% of SLE patients [5, 6] and was also associated with work disability [7]. Some studies have reported that fatigue in SLE patients is associated with disease activity, exercise, glucocorticoid use, anxiety, depression, and fibromyalgia [8-11].

In the general population, the amount and frequency of alcohol consumption are associated with a good vitality domain score in the short form 36 health survey questionnaire (SF-36) compared to the non-drinking group [12, 13]. Although several studies have suggested that alcohol consumption has a protective effect against the development of SLE [14, 15], only a few studies have examined the association between alcohol consumption and the clinical manifestation of SLE [16, 17]. One study suggested no association between alcohol consumption and fatigue in patients with SLE, but the drinking status has not been described in detail [18]. We hypothesized that, as in the general population, the amount and frequency of alcohol consumption are also associated with less fatigue in patients with SLE. Therefore, we investigated the association between the amount or frequency of alcohol consumption and fatigue in a large, multicenter Japanese cohort of patients with SLE.

Methods

Study population and data collection

Patients were recruited from the Lupus Registry of Nationwide Institution (LUNA) cohort, which consists of 10 secondary or tertiary medical institutions in Japan. All 534 patients (median age, 45 years; 87.3% female) were aged 20 years or older when providing consent and fulfilled at least four of the revised 1997 American College of Rheumatology (ACR) classification criteria for SLE. Patients gave informed consent before inclusion.

This cross-sectional study used data captured by the LUNA cohort. Exclusion criteria were age > 75 years and pregnancy. From April 2018 to September 2019, data were collected from electronic medical records, including medical interviews, physical examinations, laboratory data, SLE Disease Activity Index (SLEDAI)-2K, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI), and self-reported questionnaires, including age, sex, medications, and LupusPRO.

Exposure

The questionnaire comprised questions pertaining to the alcohol intake, including frequency of drinking, amount, and type of beverage (beer, *sake*, whisky, wine, *shochu*, and *chuhai*). *Shochu* is a traditional Japanese distilled spirit and *chuhai* is *shochu* with soda. We defined the alcohol concentration of each beverage as follows: beer 5%, *sake* 15%, whisky 40%, wine 12%, *shochu* 25%, and *chuhai* 5%. To assess the amount of pure alcohol, we calculated the alcohol amount × 0.8 (specific gravity) and converted it to grams per day (g/day) [19]. According to a previous report [20], the frequency of drinking

was divided into three groups: less than once a month as the none group, once a week or less as the moderate group, and twice a week or more as the frequent group. The daily alcohol intake was also divided into three groups: no alcohol consumption (0 g/day), moderate alcohol consumption (less than 20 g/day), and high alcohol consumption (20 g/day or more). These grouping criteria were based on the Ministry of Health, Labour, and Welfare's definition for moderate drinking in Japanese women (20 g/day of pure ethanol). Alcohol consumption in excess of 20 g/day increases the risk of lifestyle-related diseases, such as hypertension, dyslipidemia, and stroke [21].

Outcome

The outcome was the pain vitality domain score in LupusPRO [22]. LupusPRO is a disease-specific scale that assesses SLE patients' quality of life (QOL), which consists of 12 domains: lupus symptoms, cognition, lupus medications, creation, physical health, pain vitality, emotional health, body image, desires, social support, coping, and satisfaction with care. The reliability of the pain vitality domain of Japanese LupusPRO was verified with a Cronbach's alpha coefficient of 0.90 and test-retest reliability of 0.80 [23]. The pain vitality domain is highly correlated with vitality in SF-36 and well representing fatigue [22]. The pain vitality domain in LupusPRO consists of five items: "I woke up feeling worn out", "I felt pain and ache in my body", "Unable to do my usual activities due to bodily pain", "Unable to perform usual activities for a long time due to pain/fatigue", and "The kinds of tasks or activities I could perform were limited because of pain or fatigue". Each item has 5 options: "none of the time", "a little of the time", "some of the time", "most of the time", and "all of the time", with total scores ranging from 0 to 100 (a higher score indicating better QOL).

Covariates

Based on the previous reports [8] and the clinical perception of rheumatologists, covariates were determined as follows: age, sex, smoking, glucocorticoid use, hydroxychloroquine use, belimumab use, other immunosuppressant use (including cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, tacrolimus, cyclosporine, and rituximab), psychotropic use (such as hypnotics, mood stabilizers, anxiolytics, antidepressants, and antipsychotics), SLEDAI-2K score, and SDI score.

Statistical analysis

For the clinical characteristics of patients categorized by the frequency of drinking (exposure), continuous data with a normal distribution were summarized as median and interquartile range (IQR). Linear regression models were used to assess the association between alcohol intake or frequency and fatigue in unadjusted and multivariate analyses, and coefficients and 95% CIs were estimated. The effect size of the outcome was interpreted as a coefficient for the relevant frequency of drinking compared to the reference group. In the sensitivity analysis, we used multiple imputation accounting for the missing covariates. Twenty imputations were performed using the multiple imputations with chained equation methods, assuming that the analyzed data were missing at random. These estimates were combined using Rubin's rule. We analyzed the imputed missing covariate data in the same manner. All analyses were performed using the Stata software (version 17.0; Stata Corp., College Station, TX, USA). Statistical significance was set at $p < 0.05$.

Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki, and this study protocol was approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences and Okayama University Hospital (Ken2010-018). All patients provided written informed consent. Patient data were anonymized and deidentified before analysis.

Patient and public involvement

Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of the research.

Results

Patient demographics and clinical characteristics

This study included 642 patients visited between April 2018 and September 2019. The reasons for exclusion are shown in Figure 1, and Table 1 summarizes the patient demographic and clinical characteristics in this analysis.

534 patients were included in primary analysis. The median (IQR) age at inclusion was 45 (34, 55) years and 466 (87.3%) patients were female. Based on the frequency of drinking, the 534 patients were found to be distributed as follows: 326 (61.0%) – in the none group, 121 (22.7%) – in the moderate group, and 87 (16.3%) in the – frequent group. As for the amount of daily alcohol intake, the patients were found to be grouped as follows: 255 (47.7%) – no alcohol consumption, 245 (45.9%) – moderate alcohol consumption, and 34 (6.4%) – high alcohol consumption. Among the type of alcohol, beer was the most popular (n=145, 27.2%), followed by *chuhai* (n=139, 26.0%), wine

(n=46, 8.6%), whisky (n=20, 3.7%), *sake* (n=17, 3.2%), and *shochu* (n=11, 2.1%). The median SLEDAI-2K and SDI score were 4.0 (IQR 2.0, 8.0) and 1.0 (IQR 0.0, 2.0), respectively. The use of glucocorticoids, immunosuppressants, and psychotropics among patients were found to be 92% (n = 491), 62.9% (n = 336), and 22.1% (n = 118), respectively. Hydroxychloroquine was used by 222 (41.6%) patients and belimumab by 16 (3.0%) patients. Tacrolimus was the most frequently used immunosuppressive agent (n = 176, 33.0%), followed by mycophenolate mofetil (n=91, 17.0%), azathioprine (n=44, 8.2%), cyclosporine (n=38, 7.1%), methotrexate (n=12, 2.3%), and cyclophosphamide (n=4, 0.8%).

Pain Vitality

The median pain vitality domain score was 80.0 (IQR 60.0, 95.0). Figure 2 shows the distribution of the pain vitality domain score for each category of drinking, suggesting a "dose-response" relationship between the frequency and amount category and the pain vitality domain score of LupusPRO.

Primary analysis

The results of the simple regression analysis (crude) and multiple regression analysis (adjusted) are shown in Table 2 (the frequency of drinking) and Table 3 (the amount of alcohol consumption). As shown in Table 2, there was a significant association between high frequency of drinking and the high score of the pain vitality domain, indicating less fatigue. In the adjusted model, the partial regression coefficient β was 2.57 (95% CI -2.55 to 7.70) and 5.98 (95% CI 0.19 to 11.76) for the moderate group and the frequent group, respectively. In addition, as shown in Table 3, there was no association between the amount of alcohol consumption and the pain vitality domain score. In the adjusted

model, the partial regression coefficient β was 1.55 (95% CI -2.78 to 5.89) and 7.68 (95% CI -1.10 to 16.45) for <20 g/day and ≥ 20 g/day alcohol consumption, respectively.

Sensitivity analysis

After multiple imputations of missing values, the partial regression coefficient β was 5.85 (95% CI 0.28 to 11.4). This indicated a positive association between frequent group and the pain vitality domain score, similar to the results of the primary analysis.

Discussion

In this study, we attempted to validate the association between alcohol consumption habits and their effects on fatigue experienced among patients with SLE. We found that a majority of the eligible patients had little or no drinking habit and a very small percentage (6.4%) had a high alcohol consumption level, the frequency of alcohol consumption in the study population was similar to that of the general population of Japanese women [24] and the percentage of heavy drinkers was lower [24]. The frequency of alcohol consumption was positively associated with the pain vitality domain score, which indicates less fatigue, even after adjusting for potential confounders, such as smoking and consumption of glucocorticoids, psychotropics, and other immunosuppressants.

Previous studies in non-SLE populations and in more than 80,000 healthy individuals have shown that both the amount and frequency of alcohol consumption are positively correlated with vitality [12, 13, 25]. Our study showed similar results in terms of frequency of alcohol consumption. We found that the pain vitality domain score of the LupusPRO was positively associated with drinking twice a week or more. A previous study in patients with SLE has reported that alcohol consumption was not significantly associated with fatigue [18], but it was not assessed using detailed information on the amount and frequency of alcohol consumption. This may be the reason why it was difficult to show the association between alcohol consumption and fatigue.

However, we did not find an association between the amount of alcohol consumption and the pain vitality domain score in this study. Our findings might have been underpowered because only 6.4% (n=34) of patients drank more than 20 g/day. The mechanism underlying the link between alcohol consumption and vitality has not been

clarified, and inconsistent results have been reported. Interestingly, a previous report on alcoholism proposed a theory (the self-medication hypothesis) that increased alcohol consumption leads to depression and anxiety, which eventually progresses to alcohol use disorders [26, 27]. According to the self-medication hypothesis, excessive drinking may worsen vitality, as shown in the association between drinking and anxiety/depression [28, 29]. Meanwhile, a large longitudinal study in the US female population reported that the higher the alcohol dose (≥20 g/day), the better the vitality score [13]. In our cohort population, the association between heavy drinking and vitality could not be fully assessed due to a low number (6.4%) of SLE patients with heavy drinking habits. Further research is needed to confirm whether the results of this study can be applied to populations that consume excessive alcohol.

This study has several strengths. First, this is one of the few studies to examine the association between alcohol consumption and vitality in patients with SLE. Recently, the importance of HRQOL, such as vitality, has been increasingly recognized in SLE patients. Second, this research describes in detail the large collection and well-defined drinking data, such as the frequency and amount, like no other study in the SLE literature. Finally, this was a large multicenter prospective cohort study that collected the clinical data of SLE patients.

Our study has some limitations. First, there may have been a misclassification of drinking status using the questionnaire in this study. Patients may report less than what they actually drink if they drink heavily, despite their poor disease conditions. This is most likely to occur in patients with a higher frequency of alcohol consumption. Misclassification due to low drinking frequency should only bias findings towards the null, resulting in an underestimation of the association between drinking frequency and

vitality. Second, some potential confounders, such as socioeconomic status and concomitant fibromyalgia, may be present, which may have prevented us from fully accounting for the impact of these factors on pain and vitality in this cohort. Previous studies reported that fibromyalgia may be associated with fatigue [18, 30, 31]. However, the prevalence of fibromyalgia in SLE patients has been reported to be approximately 6.2% in a large cohort [32] and hence not considered to have a significant impact. Third, the use of HCQ was low, at only 41 %. The relatively short period from HCQ approval in Japan may have caused the low prescription of HCQ in this cohort. Our results may not fully apply to other cohorts with different HCQ prescription rates. Fourth, most of all participants in this study are Japanese and some beverage is available only in Japan, which may affect the generalizability of this study. Finally, because of the cross-sectional nature of our study, causal reversal is possible and further longitudinal studies are necessary to examine the relationship between drinking pattern and vitality.

In conclusion, we revealed that drinking more than twice a week was independently associated with less fatigue, except in heavy drinkers. These results encourage further investigation into whether modifiable drinking habits have any effect on fatigue as surrogate indicators of the development of important complications such as death and cardiovascular disease in patients with SLE.

Funding

No specific funding was received from anybody in the public, commercial, or not-for-profit sectors to carry out the work described in this article. This work was supported by JSPS KAKENHI (grant number JP20K18962).

Acknowledgements

We express our gratitude to Tomomi Maruyama and Tomoko Takamae for their assistance with data management. We are grateful to all collaborators working on LUNA.

Disclosure statement

KS received speaker's fee from Glaxo Smith Kline K.K. The other authors have declared no conflicts of interest with respect to this article.

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Figure Legends

Figure 1 - Flow diagram of the screening process in this study

The flow chart shows the screening process for this study's subjects.

Figure 2 - The distribution of pain vitality domain score

We used a box-and-whisker plot to describe the scores on the pain vitality domain of Japanese LupusPRO ranging from 0 to 100 (vertical axis) in the frequency and amount categories.

Abbreviation: Lupus PRO, Lupus Patient-Reported Outcome.

Table 1. Characteristics of participants, stratified by the frequency of drinking

variables	Total N=534	Frequency None* N=326	≤1 day/week N=121	≥ 2 days/week N=87
Age, median IQR, years	45.0 [34.0-55.0]	45.0 [36.0-56.0]	41.0 [31.0-49.0]	46.0 [38.0-55.0]
Sex, female, n (%)	466 (87.3)	291 (89.3)	108 (89.3)	67 (77.0)
Smoking, n (%)	58 (10.9)	29 (8.9)	14 (11.6)	15 (17.2)
SLEDAI-2K, median IQR, points	4.0 [2.0-8.0]	4.0 [2.0-8.0]	4.0 [2.0-8.0]	4.0 [2.0-6.0]
SDI, median IQR, points	1.0 [0.0-2.0)	1.0 [0.0-2.0)	0.0 [0.0-1.0)	1.0 [0.0-2.0)
Glucocorticoids, n (%)	491 (91.9)	303 (92.9)	113 (93.4)	75 (86.2)
Immunosuppressants, n (%)	336 (62.9)	198 (60.7)	86 (71.1)	52 (59.8)
Hydroxychloroquine, n (%)	222 (41.6)	124 (38.0)	64 (52.9)	34 (39.1)
Belimumab, n (%)	16 (3.0)	7 (2.1)	5 (4.1)	4 (4.6)
Antipsychotics, n (%)	118 (22.1)	78 (23.9)	22 (18.2)	18 (20.7)
Pure alcohol (g/day)				
None, n (%)	255 (47.8)	255 (78.2)	0 (0.0)	0 (0.0)
<20 g/day, n (%)	245 (45.9)	71 (21.8)	119 (98.3)	55 (63.2)
≥20 g/day, n (%)	34 (6.4)	0 (0.0)	2 (1.7)	32 (36.8)

* Defined as less than one day/month

Abbreviations: IQR, interquartile range; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 2. The association between the frequency of alcohol and the pain vitality domain score

Frequency of drinking	Crude		Adjusted*	
	β coefficient [95% CI]	P value	β coefficient [95% CI]	P value
None†	Ref		Ref	
≤1 day/week	4.25 [-0.98 to 9.48]	0.11	2.57 [-2.55 to 7.70]	0.33
≥2 days/week	7.01 [1.09 to 12.94]	0.02	5.98 [0.19 to 11.76]	0.04

† defined as less than 1 day/month ＊adjusted for age, sex, smoking, antipsychotics, SLEDAI-2K, SDI, glucocorticoids, hydroxychloroquine, immunosuppressants, and belimumab
Abbreviations: SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Table 3. The association between the amount of alcohol and the pain vitality domain score

Amount of drinking	Crude		Adjusted*	
	β coefficient [95% CI]	P value	β coefficient [95% CI]	P value
None	Ref		Ref	
<20 g/day	3.49 [-0.91 to 7.89]	0.12	1.55 [-2.78 to 5.89]	0.48
≥20 g/day	8.53 [-0.45 to 17.51]	0.06	7.68 [-1.10 to 16.45]	0.09

＊ Adjusted for age, sex, smoking, antipsychotics, SLEDAI-2K, SDI, glucocorticoids, hydroxychloroquine, immunosuppressants, and belimumab
Abbreviations: SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000, SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index