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Inflammation and fatigue in early, untreated Parkinson's Disease

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Objectives: Parkinson's disease (PD)-related fatigue is a significant clinical problem, and the pathological processes that cause fatigue remain unknown. The aim of the present study was to explore the possible association of peripheral inflammation markers and fatigue in PD.

Materials & methods: We included 47 drug naïve, newly diagnosed PD patients with low (≤3.0) or high (>5.5) fatigue levels as evaluated by the Fatigue Severity Scale (FSS). Strict diagnostic criteria were applied for inclusion. Patients with possible confounding causes for fatigue were excluded. Serum concentrations of a panel of inflammatory markers (IL-8, TNF-α, MCP1, MIP-1β, IL-6, IL-6R, p-selectin, E-selectin-1, ICAM, VCAM-1, CCL5, IL1-Ra, and TNFR1) were measured using ELISA technology in PD patients with and without fatigue to assess the potential relationships of fatigue in newly diagnosed, treatment-naïve patients.

Results: Fatigued PD patients had significantly higher levels of the IL-1 receptor antagonist (IL1-Ra) (1790 pg/mL (SD1007) vs 1262 pg/mL (SD379)) and of the adhesion molecule VCAM 1 (1071 ng/mL (SD276) vs 895 ng/mL (SD229)) than non-fatigued patients. A binary logistic regression model, including high or low FSS score as the dependent variable and UPDRS motor score, MADRS, MMSE, ESS, and IL1-Ra/VCAM-1 as independent variables, showed a significant effect both for IL1-Ra and VCAM-1.

Conclusions

Higher serum levels of the inflammatory molecules IL1-Ra and VCAM-1 were associated with higher fatigue levels in patients with newly diagnosed, drug-naïve PD. These findings highlight an altered immune response as a potential contributor to PD-related fatigue, from the earliest clinical stages of the disease.

KEYWORDS
biomarker, fatigue, inflammation, interleukin-1 receptor antagonist, Parkinson's disease, vascular cell adhesion protein-1

1 | INTRODUCTION

Parkinson's disease (PD)-related fatigue is a significant clinical problem, and fatigue is among the most common and disabling symptoms of the disease as well as a major contributor of reduced quality of life.[1] The prevalence of PD is more than 1/1000, and 2%-3% of people aged 65 years and older have PD.[2] Studies have shown that approximately half of PD patients suffer from clinically relevant fatigue.[1] The pathological processes causing fatigue remain unknown. There is no clear association with motor impairment or disease duration,[1] and the nature of the relationship between fatigue and coexisting depressive symptoms is not clear.

In addition, fatigue may be present and bothersome prior to the onset of motor symptoms.[3]

In the broader fatigue literature, a key mechanism underlying fatigue is the activation of the inflammatory cytokine network.[4] Heightened inflammation can trigger the central nervous system to induce "sickness behaviors," which are part of the behavioral phenotype of fatigue.

Neuroinflammation may play a role in PD pathogenesis.[5] In particular, proinflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-2 (IL-2), and TNF-α have been proposed to be part of an immune response to tissue damage. Inflammation may contribute to the development of both motor and non-motor symptoms.[6]

In the present study, fatigue was evaluated by the Fatigue Severity Scale (FSS) in a population-based cohort of treatment naïve, newly diagnosed patients with PD. The aim of the study was to explore the possible association of peripheral inflammation markers and fatigue in PD.

2 | MATERIAL & METHODS

2.1 | The Norwegian ParkWest Project

All the study participants were recruited from the Norwegian ParkWest Project, a population-based prospective longitudinal cohort study of de novo PD patients.[7]

2.2 | Standard protocol approvals, registrations, and patient consents

The ParkWest study was approved by the Western Norwegian Regional Committee for Medical and Health Research Ethics, and written informed consent was provided by all the participants.

2.3 | Inclusion criteria

All the patients fulfilled the Gelb diagnostic criteria[8] for PD and were untreated at the present evaluation. The inclusion criteria for the ParkWest project have previously been published.[7] The PD diagnosis was reviewed 18 months after inclusion to evaluate levodopa response according to the UK Brain Bank criteria. Of the original 212 included patients, the diagnosis of PD was confirmed in 192 cases that were accepted for the study.

2.4 | Exclusion criteria

Due to overlapping symptomatology as well as to ensure optimal validity, the following patients were excluded a priori for the purposes of the present study: patients with decreased cognitive function, defined as scores <25 on the Mini-Mental State Examination (MMSE),[9] patients with depressive symptoms, defined as scores >13 on the Montgomery-Åsberg Depression Rating Scale (MADRS)[10], and patients with excessive daytime somnolence (EDS), defined as scores >10 on the Epworth Sleepiness Scale (ESS).[11] Apathy was evaluated by the apathy subsection of the Neuropsychiatric Inventory (NPI),[12] and subjects were excluded if the frequency score multiplied by the severity score was >1.[13]

Patients were also excluded if they had other internal medical or neurological diseases, including a previous clinical history of cancer, stroke, or inflammatory, autoimmune, endocrine or infectious diseases, as well as if they regularly used anti-inflammatory drugs, anti-depressants, anti-psychotics, sedatives, or painkillers.

Finally, patients with intermediate FSS[14] scores were excluded, leaving 24 patients with a low FSS score (<3) and 23 patients with a high FSS score (>5.5), totaling 47 patients.

After excluding patients with decreased cognitive function, depressive symptoms, excessive daytime somnolence, apathy, other diseases, or relevant medications as specified, 96 patients remained eligible for the study. Of these, 49 were excluded as being intermediary, leaving 24 patients with low FSS score (FSS<3) and 23 patients with a high score (FSS>5.5). We chose to exclude those with intermediate scores so as to have two clearly defined groups to compare.

2.5 | Clinical assessment

All the patients were interviewed and examined by a trained neurologist and a study nurse. The demographic data (age, years of education, weight, and height) were collected during a semi-structured interview. Body mass index was calculated (weight/height^2). Severity of disease was assessed by the Unified Parkinson's Disease rating Scale part III (UPDRS III).[15]

Fatigue was assessed by the FSS, a 9-item self-administered questionnaire, emphasizing the functional impact of fatigue. Various aspects of fatigue, including physical, social, and mental fatigue, were rated from 1 (no problem) to 7 (highest possible score).[14] The total score is given as the mean score of all the items. The Norwegian version of the questionnaire has been validated.[16]

2.6 | Serum

Serum samples were collected on the day of the clinical assessment. All the blood samples were collected after overnight fasting, between 8 and 10 AM, to minimize confounding factors caused by circadian rhythm. Blood was collected by standard venipuncture into vacuette serum separation tubes (Greiner bio-one), inverted 5 times and incubated for 30 minutes at room temperature. After centrifugation at 1000× *g* for 10 minutes, the serum supernatant was transferred to polypropylene cryo tubes prior to freezing at −80°C awaiting batch testing. The serum sample preparation was performed by trained personnel and was identical across all the collection sites. The samples were subjected to two freeze-thaw cycles for aliquoting purposes prior to the analysis.

The following inflammatory markers and adhesion molecules were measured in the patient serum samples by ELISA with the use of Quantikine High Sensitivity kits, according to the manufacturer's

instructions (R&D Systems, Oxon, UK): interleukin(IL)-6, IL-8, tumor necrosis factor (TNF)-α, chemokine [C-C motif] ligand 5 (CCL5), IL-1 receptor antagonist (IL1-Ra), IL-6 receptor (IL-6R), TNF receptor 1 (TNFR1), monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1β, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion protein (VCAM)-1, P-selectin (CD62P), and E-selectin-1 (CD62E).

2.7 | Statistical analysis

The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) software version 21 (SPSS Inc., Chicago, Il, USA), and 2-tailed *P*-values less than .05 were considered statistically significant. Mann-Whitney *U* tests for non-normally distributed data or Student's *t* tests for normally distributed data were used to compare the continuous data. For the categorical data, Pearson's chi-squared test was used. Correlations were estimated by the Spearman's rank correlation coefficient (for non-normally distributed data) or Pearson's correlation coefficient (for normally distributed data), as appropriate. A binary logistic regression analysis (method enter) was used to evaluate the contribution of the different variables.

3 | RESULTS

3.1 | Sample characteristics

Of the 47 subjects in the study, 24 patients had low and 23 patients had high fatigue scores. The demographic and clinical characteristics of the groups are presented in Table 1. The patients with fatigue had more advanced disease, as measured by the UPDRS motor score, and scored slightly higher on the MADRS. Cognitive function, measured by the MMSE, was lower in the fatigued group. ESS scores, however, were lower in the group with fatigue, indicating less EDS.

3.2 | Circulating inflammatory markers

As shown in Table 2, the fatigued patients had significantly higher plasma IL1-Ra concentrations and higher levels of the adhesion molecule VCAM-1 than non-fatigued patients.

3.3 | Correlations

There were no correlations between IL1-Ra or VCAM-1 with age, sex, years of education, BMI, UPDRS3, MADRS, MMSE, apathy, or ESS.

3.4 | Regression analyses

A binary logistic regression model, with high or low fatigue score as the dependent variable and UPDRS3, MADRS score, MMSE score, ESS score, and the inflammation marker IL1-Ra (ng/mL) as independent variables, showed a significant effect for IL1-Ra only (odds ratio 5.49, 95% CI: 1.13-26.79, *P* = .034). A similar model using VCAM-1(ng/mL) as the independent variable showed a significant effect for VCAM-1 only (odds ratio 1.005, 95% CI 1.001-1.008, *P* = .012).

TABLE 1 Baseline demographic and clinical characteristics of incident PD patients with and without fatigue

	FSS≤3 n = 24	FSS>5.5 n = 23	
	Mean (SD)	Mean (SD)	*P* value
Age	64.9 (8.5)	65.8 (10.1)	.728
Sex	16 male/8 female	11 male/12 female	.192
Years of education	12.0 (3.5)	11.5 (3.1)	.789
BMI	25.8 (2.9)	25.3 (4.6)	.302
UPDRS3	17.8 (8.7)	24.0 (9.8)	.030
MADRS	1.8 (2.2)	4.2 (4.1)	.026
MMSE	29.0 (1.3)	28.7 (0.9)	.041
ESS	5.8 (2.0)	4.2 (2.7)	.027
Apathy (NPI)	0.08 (0.3)	0.09 (0.3)	.965

Group differences were analyzed with Student's *t* tests, Mann-Whitney tests or chi-square tests as appropriate.
BMI, body mass index; ESS, epworth sleepiness scale; FSS, fatigue severity scale; MADRS, Montgomery and Åsberg depression rating scale; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; PD, Parkinson's Disease; SD, standard deviation; UPDRS3, Unified Parkinson's Disease rating scale part 3.

4 | DISCUSSION

Fatigue is an important clinical problem in patients with PD. We demonstrated that higher levels of IL1-Ra and VCAM-1 were associated with higher levels of fatigue in early untreated PD patients without known confounding etiologies for fatigue. These two cytokines were detected in all the patients and are a characteristic of ongoing inflammatory activity in vivo.

In the development of PD as well as the associated fatigue, inflammatory activity can promote glutamate dysregulation, thereby decreasing the production of neurotrophic factors that typically support neuronal health, neuroplasticity, and neurogenesis.[17] Notably, these neurotransmitter and cellular changes alter brain activity and the neurocircuits underlying distress, motivation, and motor function.[18] The question is whether cytokines are increased as a result of the stress and tissue damage that are a consequence of PD or whether inflammation precedes the fatigue and contributes to it. Pereira et al[19] and Scalzo et al[20] both found higher IL-6 plasma levels in PD patients with fatigue compared to non-fatigued patients. Lindqvist et al[21] found significantly higher IL-6 levels in patients with PD than in healthy controls as well as an association between higher levels of both sIL-2R and TNF-α with higher Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT) scores. There is evidence to suggest that inflammation, as identified in the serum measurements, is related to PD pathology. PD patients have elevated levels

TABLE 2 Serum inflammation markers in patients with PD with and without fatigue

	FSS≤3.0 n = 24 Mean (SD)	FSS>5.5 n = 23 Mean (SD)	*P*-value
Adhesion molecules			
E-selectin-1 ng/mL	45.9 (13.1)	44.9 (23.1)	.383
ICAM ng/mL	686.3 (394.7)	760.2 (383.3)	.407
VCAM-1 ng/mL	895.4 (229.3)	1070.6 (276.1)	.020
Receptors and receptor antagonists			
IL1-Ra pg/mL	1261.8 (378.5)	1790.4 (1007.0)	.041
TNFR1 ng/mL	10.3 (2.8)	11.1 (3.5)	.413
Cytokines			
IL-8 pg/mL	39.0 (17.5)	43.9 (14.6)	.076
TNF-α pg/mL	73.1 (9.1)	76.6 (12.4)	.317
MCP-1(CCL2) pg/mL	717.0 (201.3)	761.7 (221.1)	.566
MIP-1β (CCL4) pg/mL	1028.7 (85.9)	1044.1 (161.7)	.678

Levels of P-selectin, CCL5 (RANTES), IL-6 and IL-6R were assessed but were predominantly outside the detection range of the used assays. These analytes were therefore excluded from further analysis. Group differences were analyzed with the Mann-Whitney test. CCL2, Chemokine ligand 2; CCL4, Chemokine ligand 4; CCL5, Chemokine ligand 5; FSS, fatigue severity scale; ICAM-1, Intercellular adhesion molecule 1; IL-6, Interleukin-6; IL-6R, Interleukin-6 receptor; IL-8, Interleukin-8; IL1-ra, Interleukin-1 receptor antagonist; MCP-1, Monocyte chemoattractant protein 1; MIP-1β, Macrophage inflammatory protein 1β; PD, Parkinson's disease; SD, Standard deviation; TNF-α, Tumor necrosis factor α; TNFR1, Tumor necrosis factor receptor 1; VCAM-1, Vascular cell adhesion protein 1.

of proinflammatory cytokines in the brain; indeed, inflammation contributes to neurodegeneration.[22] Mechanistically, microglia release proinflammatory cytokines, which act on the endothelium of blood-brain barrier (BBB) cells to stimulate the upregulation of adhesion molecules.[23] Accordingly, this process promotes the recruitment of T cells and monocytes, which express counter receptors, and subsequently, more cytokines are released. A proinflammatory event identified in serum can promote chronic, self-propelling neuroinflammation in the brain.[24]

It has been shown that both physical and psychological stressors can directly provoke transient increases in proinflammatory cytokines. Increased levels of plasma proinflammatory cytokines are a well-documented correlate of depressive disorders. Depression is a common feature of PD. We propose a hypothesis that anxiety, depression, and poor sleep, which are common features of PD, may lead to enhanced inflammation, which may subsequently lead to persistent fatigue. For example, cancer survivors who report persistent fatigue have more profound inflammation, as measured by cytokines after cancer treatment compared to non-fatigued cancer survivors.[25] In breast cancer survivors, it has been shown that proinflammatory cytokines, including interleukin-1 receptor antagonist (IL1-Ra), soluble tumor necrosis factor receptor Type II (sTNF-RII), and neopterin, were higher than those in breast cancer survivors who were not fatigued.[26] In another study, fatigued breast cancer survivors had higher levels of IL1-Ra and soluble interleukin-6 receptor (sIL-6r) than non-fatigued survivors.[27]

Several studies that have included pharmacologic manipulations have also provided strong evidence for the role of cytokines in cancer-related fatigue. For example, sickness behaviors including fatigue and anhedonia can be reliably produced by the administration of cytokines, including IL-6 and TNF-α.[28] Similarly, the use of a TNF-α antagonist substantially reduced fatigue in patients with refractory solid tumors, with fatigue ratings that were 50%-300% lower, depending on the time assessed, compared to those who did not receive the drug.[29] Moreover, a phase II open-label supplementation study that used antioxidants and pharmaco-nutritional support (including 3 g/d of omega-3 or *n*-3) produced an approximate 40% decrease in IL-6 and a 29% decrease in TNF-α after 2 months. During the same time period, fatigue scores decreased by 59%.[30] These and other related studies support the relationship between proinflammatory cytokines and fatigue.[31] Previous work has demonstrated that IL-6 was increased among fatigued PD patients; however, we did not find that this particular cytokine was indicative of fatigue. The association between somatic symptoms and inflammation is known in the broader neuroimmunology literature, yet discrepancies regarding which cytokines are most prognostic still exist. Different response patterns may reflect the half-lives of the respective cytokines or the differences in clearance mechanisms.[32] This variance may also simply relate to the different demographics that were examined across studies. In relation to IL-6 specifically, acute psychological stress is known to strongly impact biological pathways that contribute to the regulation of IL-6 by immune cells.[33] These pathways include the sympathetic nervous system (SNS), which is activated immediately following stress exposure, and the HPA axis, which is activated more slowly, taking 20-30 minutes from stressor onset for cortisol to reach peak levels and an hour or more to return

to prestress levels.[34] It is possible that varying levels of psychological stress when the PD patients' blood was taken is responsible for this discrepancy.

Both pharmacological interventions and dietary supplements may target inflammatory molecules and may reduce fatigue in PD patients. Nonsteroidal anti-inflammatory drugs (NSAIDs) reduced inflammatory induced depressive symptoms compared to placebo, particularly the selective COX-2 inhibitor celecoxib; patients with higher inflammation benefited most.[35] Exercise and weight reduction may also reduce PD fatigue. Exercise has been shown to improve cognition and quality of life among PD patients.[36] Physically active individuals have lower levels of inflammatory biomarkers than their sedentary counterparts. Moreover, it has been suggested that reductions in inflammation provide a possible reason for the antidepressant benefits of physical exercise.[37] We therefore hypothesize that physical exercise may also reduce fatigue in PD patients by reducing inflammatory cytokines.

The strengths of this study include a well-characterized sample of PD patients with sharply discrete fatigue levels. The strict criteria excluded comorbidities that might have confounded our findings. Weaknesses of the study include that the population was assessed only at one point in time; thus, the cytokine levels could not be monitored over time. Some patients developed fatigue, while others improved. We also do not know the relationship between serum and CSF levels of the cytokines.

In summary, fatigue in PD patients is an important health concern, and understanding its pathophysiology is of great importance. Our data suggest that inflammatory activity may play an important role in fatigue among those with PD. Comorbid depression and sleep disturbances may exacerbate inflammatory activity in PD patients. Our data provide a basis for a rational strategy for treatment approaches in which clinical responses and cytokine biomarkers, a presumed measure of physiological responses, can be measured.

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CONFLICT OF INTEREST

There are no conflicts of interest to report. All the authors approved the final article.

AUTHOR CONTRIBUTIONS

Karen Herlofson: study concept and design, acquisition of the data, analysis and interpretation of data, writing of first draft and subsequent manuscript drafts.

Cobi J. Heijnen: analysis of the serum samples, writing parts of the manuscript, critical review of the manuscript, final approval of the manuscript to be submitted.

Johannes Lange: acquisition of the data, writing parts of the manuscript, critical review of the manuscript, final approval of the manuscript to be submitted.

Guido Alves: acquisition of the data, critical review of the manuscript, final approval of the manuscript to be submitted.

Ole-Bjorn Tysnes: initiated the ParkWest study, acquisition of the data, critical review of the manuscript, final approval of the manuscript to be submitted.

Joseph H. Friedman: initiated the present study, critical review of the manuscript, final approval of the manuscript to be submitted.

Christopher P. Fagundes: study concept and design, writing of the first draft and subsequent manuscript drafts, final approval of the version to be submitted.

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REFERENCES

1. Friedman JH, Abrantes A, Sweet LH. Fatigue in parkinson's disease. *Expert Opin Pharmacother*. 2011;12:1999-2007.
2. Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of parkinson's disease. *Mov Disord*. 2003;18:19-31.
3. Herlofson K, Ongre SO, Enger LK, Tysnes OB, Larsen JP. Fatigue in early parkinson's disease. Minor inconvenience or major distress? *Eur J Neurol*. 2012;19:963-968.
4. Raison CL, Miller AH. Depression in cancer: new developments regarding diagnosis and treatment. *Biol Psychiatry*. 2003;54:283-294.
5. Rocha NP, De Miranda AS, Teixeira AL. Insights into neuroinflammation in parkinson's disease: from biomarkers to anti-inflammatory based therapies. *Biomed Res Int*. 2015;2015:628192.
6. Barnum CJ, Tansey MG. Neuroinflammation and non-motor symptoms: the dark passenger of Parkinson's disease? *Curr Neurol Neurosci Rep*. 2012;12:350-358.
7. Alves G, Muller B, Herlofson K, et al. Incidence of parkinson's disease in Norway: the Norwegian ParkWest study. *J Neurol Neurosurg Psychiatry*. 2009;80:851-857.
8. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for parkinson disease. *Arch Neurol*. 1999;56:33-39.
9. Folstein MF, Folstein SE, Mchugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
10. Montgomery S, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382-389.
11. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540-545.
12. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308-2314.
13. Pedersen KF, Alves G, Bronnick K, Aarsland D, Tysnes OB, Larsen JP. Apathy in drug-naive patients with incident Parkinson's disease: the Norwegian ParkWest study. *J Neurol*. 2010;257:217-223.
14. Krupp LB, Larocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46:1121-1123.
15. Fahn S, Elton R, Committee MOTUD. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne DB, Golstein M, eds.

Recent Developments in Parkinson's Disease. Florham Park, NJ: Macmillan Health Care Information; 1987: 153-164.
16. Lerdal A, Wahl A, Rustoen T, Hanestad BR, Moum T. Fatigue in the general population: a translation and test of the psychometric properties of the Norwegian version of the fatigue severity scale. *Scand J Public Health*. 2005;33:123-130.
17. Eyre H, Baune BT. Neuroplastic changes in depression: a role for the immune system. *Psychoneuroendocrinology*. 2012;37:1397-1416.
18. Miller AH, Haroon E, Raison CL, Felger JC. Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. *Depress Anxiety*. 2013;30:297-306.
19. Pereira JR, Santos LV, Santos RM, et al. IL-6 serum levels are elevated in parkinson's disease patients with fatigue compared to patients without fatigue. *J Neurol Sci*. 2016;370:153-156.
20. Scalzo P, Kummer A, Cardoso F, Teixeira AL. Serum levels of interleukin-6 are elevated in patients with parkinson's disease and correlate with physical performance. *Neurosci Lett*. 2010;468:56-58.
21. Lindqvist D, Kaufman E, Brundin L, Hall S, Surova Y, Hansson O. Non-motor symptoms in patients with parkinson's disease - correlations with inflammatory cytokines in serum. *PLoS ONE*. 2012;7:e47387.
22. Wahner AD, Sinsheimer JS, Bronstein JM, Ritz B. Inflammatory cytokine gene polymorphisms and increased risk of parkinson disease. *Arch Neurol*. 2007;64:836-840.
23. Reale M, Iarlori C, Thomas A, et al. Peripheral cytokines profile in parkinson's disease. *Brain Behav Immun*. 2009;23:55-63.
24. Qin L, Wu X, Block ML, et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. *Glia*. 2007;55:453-462.
25. Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. *Brain Behav Immun*. 2007;21:863-871.
26. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosom Med*. 2002;64:604-611.
27. Bower JE, Ganz PA, Aziz N, Fahey JL, Cole SW. T-cell homeostasis in breast cancer survivors with persistent fatigue. *J Natl Cancer Inst*. 2003;95:1165-1168.
28. Miller AH, Manji HK. On redefining the role of the immune system in psychiatric disease. *Biol Psychiatry*. 2006;60:796-798.
29. Monk JP, Phillips G, Waite R, et al. Assessment of tumor necrosis factor alpha blockade as an intervention to improve tolerability of dose-sensitive chemotherapy in cancer patients. *J Clin Oncol*. 2006;24:1852-1859.
30. Mantovani G, Maccio A, Madeddu C, et al. A phase 2 study with antioxidants, both in the diet and supplemented, pharmaconutritional support, progestagen, and anti-cyclooxygenase-2 showing efficacy and safety in patients with cancer-related anorexia/cachexia and oxidative stress. *Cancer Epidemiol Biomarkers Prev*. 2006;15:1030-1034.
31. Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun*. 2007;21:413-427.
32. Oliver JC, Bland LA, Oettinger CW, et al. Cytokine kinetics in an in vitro whole blood model following an endotoxin challenge. *Lymphokine Cytokine Res*. 1993;12:115-120.
33. Fagundes CP, Glaser R, Hwang BS, Malarkey WB, Kiecolt-Glaser JK. Depressive symptoms enhance stress-induced inflammatory responses. *Brain Behav Immun*. 2013;31:172-176.
34. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev*. 2000;21:55-89.
35. Kohler O, Benros ME, Nordentoft M, et al. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. *JAMA Psychiatry*. 2014;71:1381-1391.
36. Cruise KE, Bucks RS, Loftus AM, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. *Acta Neurol Scand*. 2011;123:13-19.
37. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11:607-615.

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