Industrial Health 2014, **52**, 531–534

Short Communication

Association of Psychological Stress Response of Fatigue with White Blood Cell Count in Male Daytime Workers

Naoko NISHITANI[1]* and Hisataka SAKAKIBARA[2]

[1]Department of Nursing, Sugiyama Jogakuen University, Japan
[2]Nagoya University School of Health Sciences, Japan

Received March 1, 2013 and accepted June 18, 2014
Published online in J-STAGE June 27, 2014

Abstract: Relationships between work-related psychological and physical stress responses and counts of white blood cells (WBCs), neutrophils, and lymphocytes were investigated in 101 daytime workers. Counts of WBCs and neutrophils were positively associated with smoking and inversely correlated with high density lipoprotein (HDL)-cholesterol levels. Additionally, general fatigue score as measured by the profile of mood state was positively correlated with WBC and neutrophil counts whereas lymphocyte counts was not significantly associated with fatigue score. Multiple regression analysis showed that WBC count was significantly related to general fatigue, age, and HDL-cholesterol levels. Neutrophil count was significantly related to HDL-cholesterol levels and fatigue score. Among various psychological stress response variables, general fatigue may be a key determinant of low-grade inflammation as represented by increases of WBC and neutrophil counts.

Key words: General fatigue, Psychological stress response, White blood cells, Neutrophils, Inflammation

Elevated white blood cell (WBC) count has been reported to be an independent predictor of coronary heart disease and is associated with several cardiovascular disease risk factors[1)]. Studies have reported that WBC count is a convenient and useful marker to capture inflammatory responses because it is inexpensive compared to other inflammatory markers such as interleukin-6 (IL-6) and high-sensitivity C-reactive protein (CRP), and is commonly examined during a regular workplace health checkup in Japan[2)].

Increment of WBC count has been shown to have a positive relationship with unfavorable lifestyles such as obesity, smoking, poor sleep, and unhealthy diet, which is known to contribute to cardiovascular dysfunctioning[2)]. Our previous study in Japanese male workers showed that poor sleep can be an independent risk factor for an increase in WBC count[3)]. WBC count has also been shown to have an inverse relationship with hours of work, which may have reflected poor sleep[2)]. In this study, we investigated the relationship between work-related psychological and physical stress responses, i.e., fatigue, anger, activity, tension/anxiety, depression, and WBC and its differential counts in male Japanese daytime workers.

Subjects were 213 male industry workers in one manufacturing industry who received annual workplace health examination in April 2009. During the checkup, WBC and its differential counts were determined. A self-administered questionnaire survey was distributed one week before the health examination and collected at the time of the checkup. The questionnaire included items such as age, sex, work pattern (daytime or shift work), cohabiting family members, type of work, overtime work (working

*To whom correspondence should be addressed.
E-mail: n-nishitani@sugiyama-u.ac.jp

hours per week excluding weekend or holiday work), walking time during commute, sleep duration (weekdays), habitual exercise (number of days per week), smoking status (current, past, and never, as well as quantity per day in current smokers), alcohol consumption (number of days per week), and subjective health status (very good, good, poor, very poor).

Insomnia was assessed using the Athens Insomnia Scale (AIS), an internationally used measure of insomnia[4]. The AIS, devised by the World Health Organization, is based on criteria of the International Classification of Disease 10th Revision. In this study the first five of eight AIS questions were used, because these five questions have been shown to be useful to determine poor sleep habits[4]. The Brief Job Stress Questionnaire (BJSQ), which was developed in a study commissioned by the Japanese Ministry of Health, Labor and Welfare, was used in the present study[5]. The questions included 29 items that measure job stress responses. The section on psychological stress response contained 18 items to measure positive responses (activity) and negative responses (anger, fatigue, tension/anxiety, and depression). The section on physical stress response included 11 items. For psychological stress responses, lower scores for activity and higher scores for other items indicated higher stress responses. For physical stress response, higher total scores indicated higher stress responses.

Blood test values measured at the time of the health examination were used for WBC count and differential count. The measurements were made using an Advia system (flow cytometry) on the same day as the health checkup at the Handa Medical Association (Aichi Prefecture). Blood pressure, waist circumference, HDL-cholesterol, triglycerides, and blood glucose levels were also determined during the health examination. Blood tests were conducted in a fasting condition during the 9:00–11:30 Body mass index (BMI) was calculated from height and body weight measured at the time of the health examination.

The questionnaire survey and measurements of WBC and its differentiations were performed if workers agreed to participate in this study with signed consent forms. The consent was obtained from 199 workers. People being treated for diabetes or other inflammatory conditions, as well as those working under shifts were excluded. As a result, the subjects for analysis were 101 daytime workers (age, 20–65 yr; mean, 40.7 ± 13.2 yr). This study was approved by the Nagoya University School of Medicine Ethics Committee.

Associations between basic attributes and living habits were analyzed using the *t*-test. Correlations between WBC count, neutrophil count, and lymphocyte count, and basic attributes, living habits, total AIS score, waist circumference, blood pressure, HDL-cholesterol, triglycerides, fasting blood glucose, and psychological and physical stress responses were investigated using Spearman's correlation coefficient. The results showed that HDL-cholesterol levels and the psychological stress response of fatigue were significantly correlated with WBC and neutrophil counts. Multiple regression analysis was performed for smoking, HDL-cholesterol levels, and psychological stress response of fatigue, adjusting for age and BMI. SPSS 17.0 J was used for all analyses.

Correlational analysis showed that HDL-cholesterol levels were negatively correlated with WBC and neutrophil counts ($r<-0.31$, Table 1). The psychological stress response of fatigue was found to be positively correlated with WBC ($r=0.227$) and neutrophil counts ($r=0.233$) (Table 1). No significant relationships were found between any other psychological stress responses and blood cell counts. Physical stress responses were not significantly related to the counts of WBCs, neutrophils, and lymphocytes. Multiple regression analysis was conducted for WBC and neutrophils separately, adjusting for age, BMI, and smoking status (Table 2). Results showed that white blood cell count was related to the psychological stress response of fatigue, age, and HDL-cholesterol levels. Neutrophil count was related to HDL-cholesterol levels and the psychological stress response of fatigue.

A major finding of this study is that the fatigue score (based on the 3 item version of profile of mood state) was associated with an increase of WBC which may be attributable to an increase of neutrophil counts. Several past studies may support our findings. It has been reported that CRP, a well-known inflammatory marker, is associated with an increase of fatigue in a 5 yr prospective study[6]. Another study found that higher levels of fatigue were related to a decrease in NK cells[7]. However, no relationship was found between fatigue and T cells or B cells. A systematic review demonstrated the possibility that psychological stress such as job demands and low job control may negatively impact immune responses such as NK cell activity[8]. It has also been reported that the amount of overtime (which may suggest increased fatigue symptoms due to overtime) is inversely associated with NK cell counts[9]. Additionally, it has been suggested that job stress is related to a dampened innate immune defense that may change the pattern of cytokine production[10], leading to an

Table 1. Spearman's correlation coefficients between blood cell counts (white blood cells, neutrophils, and lymphocytes) and basic attributes, living habits, psychological and physical stress responses

Characteristic	White blood cells	Neutrophils	Lymphocytes
Age (yr)	0.064	0.002	0.113
BMI (kg/m^2)	−0.023	0.020	−0.072
Overtime (h/wk)	0.101	−0.034	0.158
Mean sleeping hours	0.027	0.030	0.052
Total AIS score	0.054	0.070	0.018
Psychological stress responses (activity)	−0.116	−0.128	−0.100
Psychological stress responses (anger)	0.055	0.069	−0.070
Psychological stress responses (fatigue)	0.227 *	0.233 *	0.118
Psychological stress responses (tension/anxiety)	0.052	0.068	0.026
Psychological stress responses (depression)	0.022	0.041	−0.012
Physical stress responses	0.100	0.133	−0.036
Waist circumference (cm)	0.097	0.089	0.045
Systolic BP (mmHg)	0.026	−0.033	0.097
Diastolic BP (mmHg)	0.008	−0.023	0.077
HDL-cholesterol (mg/dl)	−0.311 **	−0.319 **	−0.164
Triglycerides (mg/dl)	0.148	0.084	0.126
Fasting blood sugar (mg/dl)	0.100	0.087	0.153

* $p<0.05$, ** $p<0.01$

Table 2. Standardized correlation coefficient (β) with white blood cell count and neutrophil count as dependent variables in multiple regression analysis

Characteristic	White blood cell count			Neutrophil count		
	β	t	*p* value	β	t	*p* value
Age (yr)	0.224	2.280	0.025	0.168	1.675	0.097
BMI (kg/m^2)	−0.071	−0.717	0.475	−0.061	−0.602	0.549
Smoking	0.156	1.620	0.108	0.135	1.369	0.174
HDL-cholesterol (mg/dl)	−0.228	−2.219	0.029	−0.220	−2.091	0.039
Psychological stress responses (fatigue)	0.231	2.331	0.022	0.203	1.999	0.048

increase of inflammatory response which could influence WBC count as well. Similarly, IL-6 levels, an important marker of chronic low-grade inflammation, have been reported to increase by sleep disorders and fatigue[11]. Collectively, these studies support the notion that fatigue may promote inflammatory response on one hand and suppression of cellular immune response on the other. Similar to previous findings, our study also showed that WBC count is positively correlated with smoking and is negatively correlated with HDL-cholesterol levels. Therefore, a work-related psychological stress response could be an additional risk for low-grade inflammatory responses in persons with smoking habit or a low HDL-cholesterol levels. In terms of the relationship between coronary artery disease and inflammation, lifestyle habits such as diet and exercise may have positive effects on inflammation[12]. The present study suggests that maintaining good mental health in addition to improving living habits may be important to prevent arteriosclerotic disease among working people. Greater support to control job stress and promoting mental and physical relaxation would be desirable in the workplace.

Our previous study indicated that poor sleep can be an independent risk factor for a higher WBC count. In that study, shift workers had higher WBC counts than daytime workers, which may be attributable to poor sleep/fatigue[3]. In another study, higher WBC counts were more frequently found in shift workers who are suffering from sleep problems compared to those without such problems[13]. However, such findings were not observed in daytime workers with sleeping problems in the present study.

There are several limitations to the present study. First, this was a cross-sectional study. Further longitudinal investigations are needed to determine the impact of changes in WBCs and neutrophils as physical indicators due to a psychological stress response. Second, the number of subjects was small, and subjects were limited to men at a single work site. Third, self-administered questionnaires were used to determine sleep duration and other living habits, AIS, and psychological and physical stress responses. Objective measurements were not made in this study. Lastly, in this study, WBCs and neutrophils were examined, but the inflammatory mechanism is complex. Further detailed investigation including cytokines and CRP levels may be necessary to investigate the impact of fatigue on potential inflammatory processes.

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