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Factors That Influence Sleep Disturbance and the Mediating Effects of Depression on Sleep Disturbance in Patients With Rheumatoid Arthritis

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Little is known about the nature of relationships between sleep disturbance and influencing factors in rheumatoid arthritis. The purpose of this study was to identify factors that influence sleep disturbance and to evaluate mediating effects of depression on sleep disturbance. A nonexperimental, descriptive, correlational study design was adopted. One hundred patients with rheumatoid arthritis were recruited. Inflammatory status and levels of pain, fatigue, functional disability, depression, and sleep disturbance were measured. The factors that directly influenced sleep disturbance were gender, rheumatoid arthritis duration, serum C-reactive protein level, fatigue, and depression. Depression was found to have mediating effects on the relationships between sleep disturbance and arthritis symptoms. Pain, fatigue, and depression were found to have significant direct or indirect impacts on sleep disturbance. Our findings may improve understanding of sleep disturbance and aid the development of effective nursing management strategies for patients with rheumatoid arthritis suffering from sleep disturbance.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that primarily affects joints but also has systemic effects (Guo et al., 2016). It is more prevalent in women than in men, and its prevalence is 0.5%–1.0% worldwide (Matcham et al., 2013; Scott et al., 2010). The most common symptoms of RA are pain, fatigue, depression, and functional disability (Oh et al., 2019). However, sleep disturbance is also a common and disturbing symptom of RA (Drewes et al., 2000). According to Guo et al. (2016), 54%–70% of RA patients experience sleep disturbance, and this may have debilitating effects on physical and psychoemotional functions and adversely affects health in RA patients.

RA patients frequently experience multiple concurrent symptoms of pain, fatigue, and depression (Oh et al., 2019). These symptoms have interrelated synergistic effects on RA outcomes (Guo et al., 2016; Luyster et al., 2011) and have been consistently reported to aggravate sleep disturbance. In addition to these symptoms, other factors have been found to influence sleep disturbance, but few studies have addressed the nature of relationships between sleep disturbance and its influencing factors in RA patients. Understanding how and why such factors impact sleep disturbance is important for developing effective nursing management strategies for RA patients with sleep disturbance. Accordingly, we developed and tested a hypothetical prediction model for sleep disturbance that included demographic and disease-related factors and major RA symptoms to identify their direct and indirect (mediation) relationships in RA (see Figure 1).

Background

RA patients experience diverse types of sleep disturbance including sleep apnea, poor sleep quality, and

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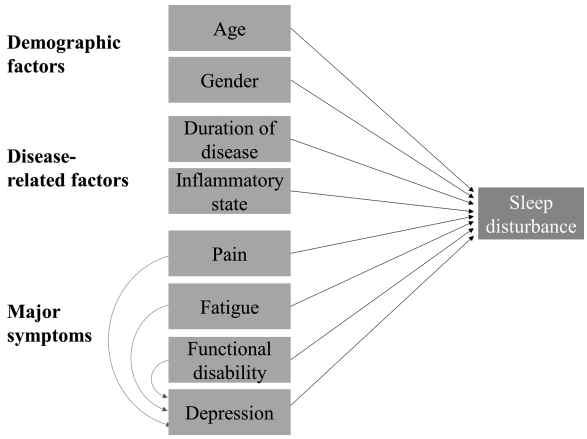

FIGURE 1. Factors that influence and mediate sleep disturbances in patients with rheumatoid arthritis.

changes in sleep patterns (Drewes et al., 2000; Iaboni et al., 2006; Reading et al., 2009; Taylor-Gjevre et al., 2009). The pathogenic mechanism of sleep disturbance in RA is considered to involve chronic activation of systemic inflammatory response and cytokine releases, which are also responsible for most of the symptoms of RA (Bourguignon et al., 2003). Accordingly, sleep disturbance is aggravated when inflammation levels rise in RA patients.

It has been suggested that major RA symptoms, such as pain, fatigue, functional disability, and depression, cause sleep disturbance (Butbul Aviel et al., 2011) and that sleep disturbance lowers RA symptom thresholds, which then further aggravate sleep disturbance (Butbul Aviel et al., 2011; Power et al., 2005). Such a vicious cycle between sleep disturbance and RA symptoms worsens disease prognoses and quality of life. In addition to RA symptoms, age, gender, duration of disease, and disease activity have been reported to contribute significantly to sleep disturbance (Abad et al., 2008; Guo et al., 2016; Sariyildiz et al., 2014; Ulus et al., 2011). Taken together, influential factors of sleep disturbance can be classified as demographic (age and gender), disease-related (disease duration and inflammatory status), and symptomatic (pain, fatigue, functional disability, and depression). Of these factors, symptoms of pain, fatigue, functional disability, and depression are known to be most influential (Guo et al., 2016; Sariyildiz et al., 2014; Ulus et al., 2011).

Patients with a chronic disease frequently experience clustered symptoms (Dodd et al., 2010; Huang & Lin, 2009; Kim et al., 2009; Oh et al., 2019). Symptom cluster is a stable combination of symptoms that co-occur in association with a specific disease and may exert synergistic effects on outcomes (Dodd et al., 2004). In patients with RA or cancer, symptoms of pain, fatigue, and depression are known to compose a symptom cluster that synergistically effects well-being and quality of life (Barsevick, 2007; Oh et al., 2019). According to the theory of unpleasant symptoms (Lenz et al., 1997) and previous findings (Katz et al., 2016; Patterson et al., 2017), symptom clusters ultimately influence diverse patient outcomes, which include functional, cognitive, and self-care abilities; activities of daily living; psychoemotional health; mortality; morbidity; medical costs; and quality of life. During a literature review of RA symptoms, it was noted that major RA symptoms appear to have individual direct and mediating effects on RA outcomes. Mediating effect involves a third variable (mediating variable or mediator) that plays an intermediate role in the relationship between independent and dependent variables (Kim et al., 2017).

Several authors have concluded that psychoemotional factors are powerful predictors of sleep disturbance in RA (Fang et al., 2019; Oh et al., 2019; Trobojević-Stanković et al., 2014; Yu et al., 2016). Notably, Oh et al. (2019) reported that RA patients with depression are 19 times more likely to have sleep disturbance. In fact, sleep disturbance is one of the many diverse symptoms of depression (Murphy & Peterson, 2015). Accordingly, it can be inferred that depression may act as a mediator of relationships between sleep disturbance and other RA symptoms.

Aims

The present study was conducted to identify factors that influence sleep disturbance and to evaluate the mediating effects of depression on relationships between sleep disturbance and major symptoms of RA. Our specific aims were (1) to determine the direct effects of demographic factors (age and gender), disease-related factors (disease duration and activity), and RA symptoms (pain, fatigue, functional disability, and depression) on sleep disturbance and (2) to examine the mediating effects of depression on the relationships between RA symptoms and sleep disturbance.

Methods

Study Design

A nonexperimental, descriptive, correlational study design was adopted to identify factors that directly or indirectly (mediating) influence sleep disturbance in RA patients.

Study Participants

One hundred RA patients were recruited by convenience sampling. All participants were RA patients being treated at a rheumatology outpatient clinic at a university hospital in Incheon (South Korea). Only patients who satisfied the following criteria were recruited: (1) rheumatologist-diagnosed RA based on diagnostic test results; (2) 19 years or older; (3) ability to understand and complete questionnaires; and (4) provision of consent after being informed of the study purposes and procedures. Patients with cognitive impairment or taking sleeping pills were excluded.

According to power analysis conducted using G*Power, the minimum sample size required was 77 (regression analysis, $\alpha = .05$, effect size = 0.18, $\alpha = .05$, power $(1 - \beta) = 0.80$, number of independent variables = 5). Effect sizes were calculated to be 0.44 or 0.56 based on the studies of Guo et al. (2016) and Sariyildiz et al. (2014), which investigated relationships between pain, depression, fatigue, and sleep disturbance.

However, it was noted that the analyses were conducted by univariate analysis and direct and indirect relationships were not analyzed in the two studies. For this reason, a more conservative effect size of 0.18 was used in the present study. Finally, 100 participants were enrolled to account for an expected loss of about 20% due to missing data or erratic responses.

Measurements

Demographic Characteristics and Health-Related Habits

Information about demographic characteristics (gender, age, marital status, and educational background) and health-related habits (current and past smoking status, duration and amount of smoking, current alcohol consumption status, frequency and amount of alcohol consumption, and type, frequency, and duration of exercise) were obtained using a self-reported questionnaire and by medical record review.

Inflammatory Status

Inflammatory status was determined using serum C-reactive protein (CRP) levels and Simplified Disease Activity Indices (SDAIs). Serum CRP levels (mg/dl) are often used as a reliable index of inflammatory status (Deutsch, 2007), particularly in patients with a chronic disease such as vasculitis or RA (Marnell et al., 2005; Nielsen, 2010). SDAIs provide an index of disease activity, and an SDAI is defined as the sum of the scores of 5 parameters, that is, the number of tender and/or swollen joints, patient and physician global assessments of disease activity. The content, criterion, and construct validity of the SDAI has been well supported (Smolen et al., 2003).

RA Symptoms

Levels of pain, fatigue, functional disability, depression, and sleep disturbance were assessed. Pain levels were measured using the numeric rating scale (NRS), which ranged from "no pain" (scored as 0) to "maximum pain" (scored as 10). The NRS has been widely used because of its good validity and reliability (Krebs et al., 2007).

Fatigue levels were measured using the 7-point, nine-item Fatigue Severity Scale (FSS) developed by Krupp et al. (1989) and translated into Korean by Chung and Song (2001). Higher FSS scores indicate more fatigue. Construct validity of the FSS was well supported by the known group method, which is a typical method to evaluate construct validity and can be supported when a test or questionnaire discriminates between two groups known to differ on the variable of interest (Davidson, 2014). Its reliability has also been verified (Cronbach $\alpha = 0.93$) (Chung & Song, 2001; Valko et al., 2008). The Cronbach α of the Korean version of the FSS used in the present study was 0.94.

Degree of functional disability was evaluated using the Stanford Health Assessment Questionnaire 8 (Stanford HAQ-8) (Uhlig et al., 2005), an abbreviated version of Stanford HAQ-22, which was originally developed to assess functional disability in RA patients. Stanford HAQ-8 is an eight-item questionnaire, and responses are rated using a 4-point Likert scale; higher scores indicate greater functional disability. HAQ-22 has been shown to be a highly valid and reliable tool (Johnson et al., 2005), and HAQ-8 is accepted to be valid based on the high correlation exhibited by HAQ-8 and HAQ-22 scores ($r = .88$) and its reliability (Cronbach $\alpha = 0.85$) (Uhlig et al., 2005). In the present study, the Cronbach α of HAQ-8 was 0.89.

Depression

Depression was evaluated using the Patient Health Questionnaire (PHQ) developed by Spitzer et al. (1999) and translated into Korean by An et al. (2013). PHQ-9 consists of nine items, which are scored using a 4-point Likert scale (ranging from 0 to 3). Overall scores range between 0 and 27, where a higher score indicates more severe depression. Construct and criterion validity of the Korean version of the PHQ has been confirmed (An et al., 2013), and its internal consistency (Cronbach $\alpha = 0.95$) and test–retest reliability ($r = .91$) were reported to be excellent. In the present study, the reliability of this tool was found to be good (Cronbach $\alpha = 0.84$).

Sleep Disturbance

Sleep disturbance was rated using the Pittsburgh Sleep Quality Index (PSQI), which was originally developed to evaluate subjective sleep quality and disturbance over the past month (Buysse et al., 1989). The PSQI demonstrated adequate construct validity based on its significant correlations with other relevant constructs in the theoretically and conceptually expected way (Bush et al., 2012; Mollayeva et al., 2016; Morin et al., 2006). Its reliability (internal consistency and test–retest reliability) was also confirmed (Hunsley & Mash, 2008; Mollayeva et al., 2016). The PSQI was translated into Korean by Sohn et al. (2012). Translation validity of the PSQI was also confirmed by Sohn et al. (2012). This tool includes seven dimensions consisting of 18 items and assesses sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disorder, use of hypnotics, and daytime dysfunction. Five additional items are rated by a bed partner or roommate (if one is available) but were not scored. Each item is scored using a 4-point Likert scale ranging from 0 (no difficulty) to 3 (severe difficulty). Overall scores range from 0 to 21, and higher scores indicate poorer sleep quality. Construct validity testing of the Korean version of the PSQI was conducted by receiver operating characteristic (ROC) curve analysis, which showed excellent sensitivity and specificity and a cutoff value for poor sleep quality of 8.5. Test–retest reliability of the Korean version of the PSQI has been reported to be good ($r = .65$, $p < .001$) (Sohn et al., 2012); in the present study, its reliability was also good ($r = .70$, $p < .001$).

Data Collection Procedure

Data collection was performed after obtaining approval from the human research committee of our university (INHAUH 2018-12-030-002), the director of the Rheumatology Department, and the president of the university hospital that provided data. All data were obtained by medical record review and using a self-reporting questionnaire. Participants read questions and selected

responses without assistance in a quiet conference room at a rheumatology outpatient center. For elderly individuals with presbyopia-associated reading difficulties, questionnaires were read by a data collector. Because subjects responded directly to the questionnaire, we believe this process did not introduce bias. The average time taken to complete the whole questionnaire package was 15–20 minutes. Each subject was given a small gift (household supplies) after questionnaire completion so as not to influence subject decision making regarding withdrawal from the study at any time.

Data Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Win 23 (IBM-Data Solutions, Seoul, South Korea). Subject demographics and disease-related characteristics and major variables were subjected to descriptive analysis. Reliabilities of measurement tools were mostly determined using the Cronbach α. Multiple regression analysis was used to identify factors that influenced sleep disturbance, and Baron and Kenny's (1986) mediation analysis was used to identify the mediating effects of depression on relationships between sleep disturbance and pain, fatigue, and functional disability.

The hypothetical model devised in the present study was tested using the three-step multiple regression analysis method proposed by Baron and Kenny (1986). The first regression step was to test whether independent variables (pain, fatigue, and functional disability) had significant impacts on the mediating factor (depression). The second regression step was to test whether independent variables had significant impacts on dependent variable (sleep disturbance). The third regression step involved testing to determine whether independent variables had significant impacts on sleep disturbance after depression was included in the models. To support mediating relationships in the hypothetical model, the first and second regressions should be significant. The third regression was used to determine whether depression was a complete or partial mediator of relationships between fatigue, pain, or functional disability and sleep disturbance. When the first two conditions were met but the third regression was not significant, depression was considered a complete mediator of these relationships. On the other hand, when the first two conditions were met and the third regression was significant but the influence of an independent variable on sleep disturbance was lessened, depression was considered to be a partial mediator (Baron & Kenny, 1986). Sobel's test was used to determine the significances of the mediating effects of depression.

Ethical Consideration

All study participants were assured they had the right not to participate and withdraw from the study without prejudice at any stage. In addition, study participants were informed beforehand about study purposes and procedures and assured personal information would remain confidential and that data would be published as means and ranges. Written informed consent was obtained from all study participants.

Results

Descriptive Statistics of Subject Characteristics and Major Variables

The mean age of 100 study participants was 55.64 ± 11.13 years (see Table 1). Eighty-one (81.0%) participants were female. Regarding educational backgrounds, 73 (73.0%) participants were educated up to high school level or higher and 27 (27.0%) up to middle school level or less. Sixty (60.0%) participants were employed. With regard to health-related habits, 97 (97.0%) were current nonsmokers and 76 (76%) were found to consume alcohol. Fifty-two (52.0%) performed regular exercise at a mean frequency of 3.46 ± 1.75 times/week for a mean

Table 1. Descriptive Statistics of Demographic, Disease-Related, and Major Variables ($N = 100$)

Variables	*n* (%)/Mean ±*SD*
Age (years)	55.64 ± 11.13
Gender	
Male	19 (19.0)
Female	81 (81.0)
Educational background	
Middle school level or less	27 (27.0)
At least high school level	73 (73.0)
Job	
Yes	60 (60.0)
No	40 (40.0)
Smoking	
Yes	3 (3.0)
No	97 (97.0)
Alcohol consumption	
Yes	76 (76.0)
No	24 (24.0)
Exercise	
Yes	52 (52.0)
No	48 (48.0)
Frequency of exercise (times/week)	3.46 ± 1.75
Duration of exercise (minutes/session)	70 ± 45.15
Body mass index (kg/m^2)	22.99 ± 3.17
Duration of rheumatoid arthritis (months)	12.04 ± 10.46
Inflammatory status	
Serum C-reactive protein (mg/L)	0.53 ± 1.22
Simplified Disease Activity Index	15.68 ± 10.62
Pain score	3.74 ± 2.55
Fatigue score	28.26 ± 14.54
Functional disability score	0.24 ± 0.41
Depression score	16.25 ± 6.01
Sleep disturbance score	6.97 ± 3.70

duration of 70 ± 45.15 minutes/session. Mean body mass index (BMI) was 22.99 ± 3.17 kg/m². Mean disease duration after diagnosis was 12.04 ± 10.46 months. Mean serum CRP level was 0.53 ± 1.22 mg/dl (normal: 0.00–0.49 mg/dl), which was relatively high. Mean SDAI was 15.68 ± 10.62 out of 86, which represented a medium level of disease activity. Of the 100 participants, eight (8%) were in remission and 92 (92%) were in an active inflammatory state; of these, 28 (28%) were in a mild inflammatory state (3.4–11.0 mg/dl), 47 (47%) were in a moderate activity state (11.1–26.0 mg/dl), and 16 (16%) were in a high activity state (26.1–86.0 mg/dl). Mean pain score was 3.74 ± 2.55 out of 10, and mean fatigue score was 28.26 ± 14.54 out of 45, and these scores represented below medium levels of pain or fatigue. Mean functional disability and sleep disturbance scores were 9.95 ± 3.30 out of 32 and 6.97 ± 3.70 out of 21, respectively, which represented mild levels of both (see Table 1).

Factors Influencing Sleep Disturbance

Prior to multiple regression analysis, the presence of multicollinearity was checked by comparing correlation coefficients of predictors (i.e., age, gender, duration of disease, serum CPR level, SDAI, pain, fatigue, functional disability, and depression). Multicollinearity refers to the condition in which two or more independent variables are highly correlated with one another in a multiple regression model. Multicollinearity is a problem because it undermines the statistical significance of an independent variable. Logarithmical transformation has been frequently adopted to reduce multicollinearity (Vatcheva et al., 2016). Our results indicated the presence of multicollinearity between SDAI and pain and between fatigue and depression (correlation coefficients: .63–.70). Accordingly, these four variables were logarithmically transformed to reduce multicollinearity and thereafter were applied to regression.

The results of multiple regression analysis indicated five significant factors that influenced sleep disturbance with a combined explicability of 41% (R^2= .41, F = 7.21, $p < .001$), that is, gender (β = .18, t = 2.06, p = .022), disease duration (β = .21, t = 2.32, p = .012), serum CRP level (β = .20, t = 2.18, p = .017), fatigue (β = .22, t = 1.71, p = .046), and depression (β = .41, t = 3.07, p = .003) (see Table 2). More specifically, sleep disturbance was more prevalent in women and in those with longer RA duration after diagnosis, a high serum CRP level, severe fatigue, or severe depression. On the other hand, age (t = 0.92, p = .180), SDAI (t = 1.145, p = .076), pain (t = 1.25, p = .108), and functional disability (t = 0.14, p = .435) were not found to have significant direct impacts on sleep disturbance.

Mediating Effects of Depression

The mediating effects of depression on relationships between sleep disturbance and RA symptoms were analyzed using three-step multiple regression analysis proposed by Baron and Kenny (1986).

Mediating Effect of Depression on the Relationship Between Pain and Sleep Disturbance

First and second regressions demonstrated pain significantly impacted depression (β = .43, t = 4.29, $p < .001$) and sleep disturbance (β = .30, t = 2.80, p = .006) (see Table 3, Figure 2A). Accordingly, the condition regarding the mediating effect of depression on the relationship between pain and sleep disturbance was met. Third regression was performed to determine the relationship between pain and sleep disturbance when depression was included in the model. This analysis showed depression significantly impacted sleep disturbance after pain was controlled (β = .51, t = 4.96, $p < .001$). On the other hand, the impact of pain on sleep disturbance was markedly reduced (β = .30 → .09) and nonsignificant (β = .09, t = 0.85, p = .395) after depression was controlled. These results indicated that depression acted as a complete mediator of the relationship between pain and sleep disturbance (see Table 3, Figure 2A).

Mediating Effect of Depression on the Relationship Between Fatigue and Sleep Disturbance

First and second regressions showed fatigue significantly impacted depression (β = .72, t = 10.16, $p < .001$) and sleep disturbance (β = .52, t = 5.98, $p < .001$) (see Table 3, Figure 2B). Therefore, the conditions regarding the mediating effect of depression on the relationship between fatigue and sleep disturbance were met. Third regression showed depression had a significant impact on sleep disturbance after fatigue was controlled (β = .39, t = 3.29, $p < .001$), and although the impact of fatigue on sleep disturbance was reduced (β = .52 → .25), it remained significant (β = .25, t = 2.09, p = .039) after depression was controlled. These results indicated depression partially mediated the relationship between fatigue and sleep disturbance (see Table 3, Figure 2B).

Table 2. Factors That Influence Sleep Disturbance

Variables	Adjusted R^2	F (p)	β	t (p)
Gender			.18	2.06 (.022)
Duration of rheumatoid arthritis	.41	7.21 (<.001)	.21	2.32 (.012)
Serum C-reactive protein			.20	2.18 (.017)
Fatigue			.22	1.71 (.046)
Depression			.41	3.07 (.003)

Note. p value represents one-tailed test value.

Table 3. Mediating Effects of Depression on the Relationships Between Major Rheumatoid Arthritis Symptoms and Sleep Disturbance ($N = 100$)

Regression Analysis	*B* (*SE*)	β	*t* (*p*)	Adjusted R^2	*F* (*p*)
Mediating effects of depression on the relationship between pain and sleep disturbance					
Step 1: Pain → Depression	.25 (.06)	.43	4.29 (<.001)	.17	18.44 (<.001)
Step 2: Pain → Sleep disturbance	.27 (.10)	.30	2.80 (.006)	.08	7.83 (.006)
Step 3: Pain/Depression → Sleep disturbance				.29	17.35 (<.001)
Pain → Sleep disturbance	.08 (.09)	.09	.85 (.396)		
Depression → Sleep disturbance	.81 (.16)	.51	4.96 (<.001)		
Mediating effects of depression on the relationship between fatigue and sleep disturbance					
Step 1: Fatigue → Depression	.43 (.04)	.72	10.16 (<.001)	.51	103.28 (<.001)
Step 2: Fatigue → Sleep disturbance	.55 (.09)	.52	5.98 (<.001)	.27	35.80 (<.001)
Step 3: Fatigue/Depression → Sleep disturbance				.34	25.14 (<.001)
Fatigue → Sleep disturbance	.26 (.13)	.25	2.09 (.039)		
Depression → Sleep disturbance	.68 (.21)	.39	3.29 (.001)		
Mediating effects of depression on the relationship between disability and sleep disturbance					
Step 1: Disability → Depression	.37 (.13)	.29	2.96 (.004)	.07	8.77 (.004)
Step 2: Disability → Sleep disturbance	.39 (.23)	.17	1.65 (.103)	.02	2.72 (.103)
Step 3: Disability/Depression → Sleep disturbance					
Disability → Sleep disturbance					
Depression → Sleep disturbance					

Because a basic condition of mediating effect of depression was not satisfied, Step 3 regression was not further conducted.

Mediating Effect of Depression on the Relationship Between Functional Disability and Sleep Disturbance

First regression indicated that functional disability had a significant impact on depression, but second regression showed it did not significantly impact sleep disturbance (β = .17, t = 1.65, p = .103; see Table 3, Figure 2C), which indicated depression did not mediate the relationship between functional disability and sleep disturbance.

Discussion

In the present study, the level of sleep disturbance in RA patients was mild (mean sleep disturbance score 6.97/21). Similarly, previous studies have reported that sleep disturbance scores (also measured using the PSQI) ranged from 5.62 to 7.93 in RA patients (Guo et al., 2016; Son et al., 2015). In comparison, sleep disturbance scores of healthy individuals have been reported to range from 3.57 to 3.88, which appear to be obviously lower than those of RA patients. According to Grandner et al. (2006), mean sleep disturbance scores in healthy young and in healthy middle-aged and elderly adults were 4.07 and 3.92, respectively.

Factors That Directly Influenced Sleep Disturbance

The factors found to influence sleep disturbance directly were gender, RA duration, serum CRP level, fatigue, and depression. On the other hand, age, SDAI, pain, and functional disability did not significantly influence sleep disturbance. With respect to gender, our findings indicated that sleep disturbance was more prevalent in women. Similarly, it has been reported that healthy women are more likely to experience sleep disturbance than healthy men (Lee, 2001). This gender difference may be explained by the effects of sex hormones on sleep, as suggested by Da Silva and Hall (1992).

RA duration after diagnosis was also found to influence sleep disturbance directly. However, previous studies have reported no relation between the two (Sariyildiz et al., 2014; Son et al., 2015). We speculate that this discrepancy is partly due to RA duration differences between studies as RA durations were 3–4 years in previous studies and only 12 months in the present study.

RA manifests as cycles of relapse and remission that depend on degrees of inflammatory response, and the pathogenic mechanism of sleep disturbance in RA is believed to involve inflammatory response and cytokine release (Westhovens et al., 2014). These relations caution that inflammatory conditions should be accurately assessed before treatment planning for RA patients. Inflammatory conditions are commonly evaluated using serum inflammatory markers or disease activity measures (Marnell et al., 2005). We used serum CPR and SDAI scores as indices of inflammatory status and found serum CRP significantly influenced sleep disturbance and that SDAI did not. However, previous studies have reported SDAI significantly predicts sleep disturbance in RA patients (Fragiadaki et al., 2012; Rajalingam

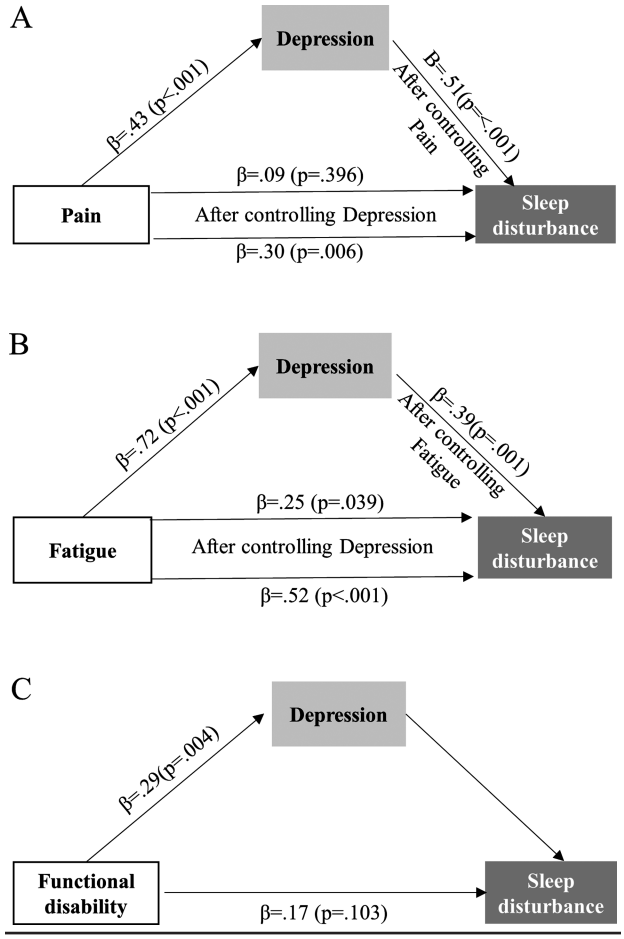

Figure 2. Mediating effects of depression. (A) Complete mediating effect of depression on the relationship between pain and sleep disturbance. (B) Partial mediating effect of depression on the relationship between fatigue and sleep disturbance. (C) No mediating effect of depression on the relationship between functional disability and sleep disturbance.

et al., 2017; Sariyildiz et al., 2014; Son et al., 2015; Westhovens et al., 2014). Further studies are needed to explain this discrepancy and to clarify the relationship between inflammatory status and sleep disturbance.

RA patients frequently experience fatigue and depression, and our findings show these two symptoms directly impact sleep disturbance, which concurs with previous reports (Guo et al., 2016; Ulus et al., 2011). These observations highlight the importance of psychoemotional and physical symptom management when addressing sleep disturbance and the need for comprehensive intervention that includes psychoemotional strategies for RA patients with sleep disturbance.

It is generally accepted that pain has a major influence on sleep, but our analysis showed pain did not directly impact sleep disturbance. This result might have been due to the simultaneous inclusions of other significant factors, such as fatigue and depression, in the analysis. We suggest additional studies be conducted to clarify the nature of the relationship between pain and sleep disturbance in RA.

Bourguignon et al. (2003) reported functional disability is one of the most frequent symptoms of RA and that it is a cause of sleep disturbance. According to Pehlivan et al. (2016), functional disability significantly impacts sleep quality in RA patients. However, we did not find this to be the case. We attribute this disparity to different degrees of functional disability among participants, as this was lower in our study than in previous studies.

Mediating Effects of Depression on the Relationships Between Sleep Disturbance and Major RA Symptoms

Of the major RA symptoms tested, pain was found to have an indirect impact on sleep disturbance via the mediating effect of depression, which agrees with that reported by Westhovens et al. (2014). Our analysis showed depression was a complete mediator of the relationship between pain and sleep disturbance. Smith and Haythornthwaite (2004) reported that patients with little pain also had sleep disturbance and suggested depression might have a mediating effect on this relationship. Because of the clustering effect of pain and depression, as shown in previous studies (Barsevick, 2007; Oh et al., 2019), it would appear that simultaneous management of pain and depression potentially offers a more effective means of relieving sleep disturbance.

The present study also showed that depression significantly mediated the relationship between fatigue and sleep disturbance. Because fatigue was found to have a significant impact on sleep disturbance regardless of the mediating effect of depression, depression was considered a partial mediator of this relationship. That is, fatigue has a direct effect on sleep and also exerts an indirect effect on sleep disturbance through its relationship with depression. Our findings support the existence of a symptom cluster composed of fatigue and depression. We emphasize the importance of managing clusters of symptoms simultaneously, that is, collective symptom management, to relieve sleep disturbance in RA.

With respect to study limitations, the results of the present study are limited in terms of their general applicability because data collection was limited to one university hospital. Accordingly, large-scale and multicenter studies are needed to obtain more robust evidence regarding factors that influence sleep disturbance in RA patients. In particular, further studies are required to clarify the nature of interrelationships between factors that influence sleep disturbance in RA.

Conclusions and Nursing Implications

In the present study, gender, RA duration, serum CRP level, fatigue, and depression were found to impact sleep disturbance directly. That is, sleep disturbance was more prevalent in women and in those with longer RA duration, severe inflammatory status, fatigue, or depression. However, age, SDAI score, pain, and functional disability did not directly impact sleep disturbance. Depression was a complete mediator of the relationship between pain and sleep disturbance and acted

as a partial mediator of the relationship between fatigue and sleep disturbance. On the other hand, depression did not have a significant mediating effect on the relationship between functional disability and sleep disturbance.

It has been shown that RA patients frequently experience concurrent symptoms of pain, fatigue, and depression (Oh et al., 2019). Our findings demonstrated that the three RA symptoms significantly influenced sleep disturbance: Fatigue and depression had a direct impact on sleep disturbance, whereas pain had an indirect impact through its association with depression (mediator). Clarification of the factors that influence sleep disturbance and of their complicated direct and indirect relationships is important to understand symptom synergism on sleep in RA. Furthermore, this information can be useful when developing effective symptom management strategies or self-management intervention programs for RA patients with sleep disturbance.

RA is a quality-of-life concern because of its chronic nature and the lack of a permanent cure and therefore nursing interventions for RA patients often aim to improve quality of life. Based on the facts that major RA symptoms have significant synergistic effects on quality of life (Oh et al., 2019) and are closely linked to sleep disturbance as shown in the present study, we recommend for rheumatology nurses to manage RA symptoms simultaneously, that is, collective symptom management, to improve quality of life, particularly sleep-related quality of life. Such comprehensive interventions incorporating physical and psychoemotional symptom management are expected to be more efficient in achieving the goals of promoting quality and cost-effective nursing care, which are the ultimate goals of nursing care.

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