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Circadian Rest/Activity Rhythms in Knee Osteoarthritis with Insomnia: A Study of Osteoarthritis Patients and Pain-Free Controls with Insomnia or Normal Sleep

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Abstract

Aberrant circadian rest/activity rhythms (RARs) may promote poor aging-related health outcomes. Osteoarthritis and chronic insomnia are common age-related conditions, but the circadian RARs of each group have not been well characterized or compared. We evaluated actigraphic RARs in individuals with: (1) knee osteoarthritis (KOA) only; (2) chronic insomnia only; (3) KOA + insomnia; and (4) pain-free good sleepers. Compared to participants with KOA only, those with KOA + insomnia had less robust RARs. There were no differences between other groups. Further research is needed to evaluate whether aberrant RARs contribute to arthritis symptoms and insomnia in KOA, and whether strengthening RARs ameliorates arthritis symptoms.

Keywords

actigraphy; sleep; activity; pain; aging

Introduction

Findings from recent epidemiologic studies suggest that altered circadian rest/activity rhythms (RARs), measured by wrist actigraphy, are associated with poor health outcomes among older adults. Lower-amplitude RARs have been linked to incident cardiovascular disease (Paudel, Taylor et al., 2011) and lower amplitude, less robust, and delayed RARs have been shown to predict incident mild cognitive impairment and dementia in older women (Tranah, Blackwell et al., 2011). Further, less robust and more advanced RARs are associated with an increased risk of mortality in older men (Paudel, Taylor et al., 2010), and

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Declaration of Interest

Potential conflicts related to this interest are managed by the Johns Hopkins University Conflict of Interest Office.

delayed RARs, and lower RAR amplitude, mean, and robustness, are associated with a greater risk of mortality in older women (Tranah, Blackwell et al., 2010). To the extent that weak or desynchronized (e.g., delayed) circadian RARs contribute to adverse health outcomes, their modification may hold promise as a means of protecting health in the growing population of older adults. This possibility highlights the need to identify populations of older adults at an elevated risk for aberrant circadian RARs. Older adults with knee osteoarthritis and/or chronic insomnia may be populations at particular risk for RAR abnormalities.

Knee osteoarthritis (KOA) is characterized by loss of cartilage in the knee, is associated with pain and mobility limitation, and affects approximately one third of older adults (Felson, Naimark et al., 1987). Insomnia is commonly defined as a subjective report of problems initiating or maintaining sleep, or non-restorative sleep, and like KOA, is common in later life; almost half of older people have insomnia complaints (Ohayon, 2002). In addition, KOA and insomnia frequently co-occur (Wilcox, Brenes et al., 2000), and pain has been shown to explain the association between KOA and insomnia (Power, Perruccio et al., 2005). Moreover, KOA and insomnia may have a synergistic relationship, such that knee pain worsens sleep, which increases pain sensitivity, and so on (Smith, Quartana et al., 2009).

To evaluate the extent to which older adults with KOA might be at an increased risk for poor health outcomes associated with abnormal circadian RARs, we compared actigraphic RARs among four groups differing by KOA and insomnia status. We hypothesized that participants with KOA or insomnia would have weaker RARs compared to those with neither of these conditions, and that those with both conditions would have the weakest RARs.

Materials and Methods

Participants

We studied participants who were screened for eligibility for a two-phase study of insomnia in KOA (NIAMS/NIH 5R01AR054871 and 5R01AR059410, MTS). Prospective participants were evaluated using a structured clinical interview for sleep disorders (Schramm, Hohagen et al., 1993) and classified according to established “insomnia” and “normal sleeper” research diagnostic criteria using data from interviews, questionnaires and polysomnography (PSG) (Edinger, Bonnet et al., 2004). Normal Sleepers were required to be free from sleep disorder diagnosis (including circadian rhythm disorders), to have Insomnia Severity Index (ISI) scores <10 (Bastien, Vallieres et al., 2001), Epworth Sleepiness Scale (ESS) scores <10 (Johns, 1991) and a Pittsburgh Sleep Quality Index (PSQI) Global score < 5 (Buysse, Reynolds et al., 1989). Patients meeting criteria for insomnia were required to report either sleep latencies or wake after sleep onset time >30 minutes, at least 3 times per week for at least one month. Prospective participants were classified as having KOA or not having KOA based on the following criteria: knee osteoarthritis according to American College of Rheumatology criteria (Altman, Asch et al., 1986); a Kellgren/Lawrence scale score 1 for at least one knee (Kellgren & Lawrence,

1957); and knee pain ratings of at least 2 (out of 10) for >4 days per week and for 6 months or longer.

Participants were excluded if they reported acute or unstable medical conditions according to a medical history questionnaire, specific psychiatric disorders (i.e., dementia, psychotic disorders) or substance abuse, measured by the Structured Clinical Interview for DSM-IV, Patient Questionnaire-extended (First, Spitzer et al., 1997), or elevated depressive symptoms (i.e., score >27) on the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). Individuals reporting specific pain disorders other than KOA were excluded. In addition, participants were excluded if they had a Mini-Mental State Exam score <24 (Folstein, Folstein et al., 1975) or tested positive on a urine toxicology screening for sedative hypnotics (benzodiazepine receptor agonists), opioids or common recreational drugs of abuse (e.g., cocaine). Further, participants completed a single night of unattended (in-home) PSG (Safiro polygraph, Compumedics, Abbotsford, Australia), and were excluded from participation if they had an apnea-hypopnea index ≥ 15 or ≥ 15 periodic limb movements with arousals per hour of sleep.

There were 312 people who completed baseline actigraphy measures, of whom 112 were excluded according to the criteria above. Thus, our sample consisted of 200 adults aged 41 and over who completed baseline actigraphy. Actigraphy data were not considered in determination of eligibility. Of the participants included in the present analyses, 28 had KOA only, 30 had insomnia only, 114 had both KOA and insomnia, and 28 good sleeper controls had neither KOA nor insomnia. Participants provided written informed consent upon enrollment, and the study protocol was approved by the Johns Hopkins Medical Institutions Institutional Review Board.

Wrist Actigraphy

All participants were asked to complete two weeks of continuous monitoring using the Actiwatch-2 wrist actigraph (Philips-Respironics, Bend, OR, USA). We accepted a minimum of five days of data. These devices were worn on the non-dominant wrist, and participants were instructed to remove them when swimming or bathing. Data were collected in 60-second epochs. Participants also used personal digital assistants (PDAs) to complete time-stamped sleep diaries each morning upon waking. These data were used to edit and score actigraphic sleep data, but were not considered in the circadian RAR analyses employed in the present study. Actigraphy data were uploaded to a PC running Actiware software (version 6.00, Philips-Respironics, Bend, OR, USA). Raw activity count data were subsequently exported and then imported into SAS version 9.3. (SAS Institute, Cary, NC). Within SAS, we used an extended cosinor approach to quantify circadian RAR (Marler, Gehrman et al., 2006). We studied four circadian parameters: amplitude, a measure of the distance from RAR peak to trough; midline estimating statistic of rhythm (MESOR), the mean of the RAR; acrophase, or the estimated time of the peak of the RAR based on the extended cosinor model; and *F*-statistic, a measure of the robustness, or strength of the RAR within and across 24-hour intervals, with higher values representing more robust rhythms (Ancoli-Israel, Cole et al., 2003; Marler, Gehrman et al., 2006).

Other Measures

Participants provided demographic data upon enrollment. They reported their weight and height at the study baseline, permitting calculation of body mass index (BMI; kg/m²). During screening visits, patients also completed the abovementioned measures of sleep (ISI, ESS, PSQI) and depressive symptoms (CES-D), the State-Trait Anxiety Inventory (Spielberger, Gorsuch et al., 1983). For two weeks, each evening before retiring to bed, participants were asked to complete an average pain rating for the day on a visual analog scale (0 = no pain, 100 = worst pain imaginable) using the PDA device. Specifically, they moved a sliding bar on the PDA screen to the position along a scale on that best represented their pain level. Visual analog scale scores were averaged across days.

Statistical Analyses

We compared chronic insomnia/KOA groups using analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variable and chi² or Fisher's exact tests for categorical variables. We then used multivariate analyses of variance (MANOVA), to determine whether circadian RAR parameters differed by chronic insomnia/KOA status, followed by pairwise comparisons adjusted for multiple testing with the Sidak correction. When we observed between-groups differences in circadian rhythm parameters, we performed hierarchical multiple regression analyses to investigate whether demographic or clinical variables (i.e., BMI, depressive symptoms, pain) explained between-group differences. Specifically, in Step 1, we entered group (i.e., the group(s) that differed by a given circadian variable); in Step 2, we entered group, age, race, and sex; and in Step 3, we entered these variables as well as BMI, CES-D score, and pain. These analyses were conducted using SPSS Version 21 (IBM Corporation).

Results

Participants had a mean $\pm$ standard deviation age of 60.2 $\pm$ 9.3 years (Table 1). Most participants (71%) were women and 36.5% were African American. Differences between the chronic insomnia/KOA groups were evident for age and BMI. Participants with KOA only were more likely to be older than all other participants ($p = 0.001$), and participants with KOA + insomnia had a significantly higher BMI than participants without a KOA diagnosis ($p = 0.001$). Overall, 158 participants (79%) completed two weeks of wrist actigraphy. Of the remaining 42 participants, 41 (98%) completed 7–13 days of actigraphy; 1 participant completed 5 days.

The omnibus test of the multivariate group effect was not significant (Wilks' Lambda = .913, $p = .123$). Participants in the four groups did not significantly differ in terms of amplitude, acrophase, or MESOR (Table 2). However, the groups had significantly different F -statistic values ($p = 0.015$). Individual between-groups tests revealed a significant difference between the KOA only and KOA + insomnia groups; those in the KOA only group had markedly higher F -statistics, compared to those with KOA + insomnia. This difference remained significant after Sidak correction for multiple testing. No other groups differed significantly in F -statistic values.

To investigate whether demographic or clinical variables explain the differences in F -statistic between the KOA only and the KOA + insomnia groups, we performed a hierarchical linear regression analysis with F -statistic as the dependent variable (Table 3). Group status (KOA + insomnia vs. KOA only) was associated with the F -statistic in Step 1 ($p = 0.004$). After adding age, race, and sex in Step 2, only group status and race were significantly associated with the F -statistic. After further adjustment for the clinical variables of BMI, CES-D, and pain (visual analog scale), group status was no longer associated with the F -statistic ($p = 0.17$), suggesting that these clinical variables explain the difference in circadian rhythm strength that we observed between these two groups.

Discussion

In this study of circadian RARs in individuals meeting criteria for KOA and/or chronic insomnia or normal sleep, we found that participants with KOA + insomnia had less robust circadian RARs, as measured by the F -statistic, compared to those with KOA alone. In addition, we found that clinical variables—namely, BMI, pain, and depressive symptoms—explained the difference we observed in this circadian parameter. To our knowledge, this is the first study comparing the circadian rhythms of individuals meeting clinical criteria for KOA, insomnia, both conditions, or neither condition.

It has been known for some time that insomnia can result from circadian rhythm disturbances, such as delayed or advanced sleep phase. Adults with sleep-onset insomnia have been shown to have phase delays in circadian rhythms of temperature (Morris, Lack et al., 1990), and interventions targeting circadian phase may relieve insomnia symptoms in those with delayed sleep phase (Czeisler, Richardson et al., 1981). Less is known, however, about circadian rhythms in the general population of older insomniacs (i.e., those without particular phase-related complaints), or those who enroll in clinical trials of insomnia treatment. Prior research using wrist actigraphy has shown that, compared to community-dwelling older adults without insomnia, those with insomnia have lower-amplitude activity during the day (a period typically characterized by greater activity) and greater activity at night (a period in which there is typically less activity) (Pollak, Perlick et al., 1992). Here, we did not find statistically meaningful differences in objectively measured RARs between middle-aged and older adults with chronic insomnia (but without KOA) and normal-sleeping control participants, perhaps because participants were not recruited on the basis of particular insomnia presentations (e.g., sleep-onset, sleep-maintenance insomnia).

Numerous studies describe circadian rhythms of various physiological processes in rheumatoid arthritis (Cutolo & Masi, 2005), an autoimmune disease distinct from osteoarthritis. However, much less is known about circadian rhythms in osteoarthritis. Existing studies indicate that osteoarthritis symptoms appear to follow circadian patterns, with pain and stiffness lowest in the latter part of the afternoon or the evening (Allen, Coffman et al., 2009; Bellamy, Sothorn et al., 1990; Bellamy, Sothorn et al., 2002), and in a recent actigraphy study of the oldest old, participants with the smallest difference between their most active and least active five-hour periods (i.e., those with the flattest RARs) were significantly more likely to have arthritis (Anderson, Catt et al., 2014). While we did not find any differences in acrophase between participants with or without KOA and/or

insomnia, we found that those with KOA + insomnia had less robust rhythms, measured by a lower F -statistic, compared to normal-sleeping individuals with KOA. Notably, and perhaps, somewhat surprisingly, we did not find a significant difference in the F -statistic when comparing the normal sleeper group with the primary insomnia group, although the difference between these groups was in the expected direction, with the primary insomnia group demonstrating less robust rhythms compared to normal sleeping controls. We are not aware of any other studies reporting the F -statistic in patients meeting criteria for primary insomnia. Though not statistically significant, it is also interesting to note that the normal-sleeping patients with KOA had the highest F -statistic values compared to any group. This warrants investigation in future studies of circadian RARs in KOA.

Our findings have two primary implications. First, because a reduced F -statistic is associated with an increased risk of cognitive impairment (Tranah, Blackwell et al., 2011) and mortality (Tranah, Blackwell et al., 2010), lower RAR robustness may increase the risk of these outcomes among middle-aged and older adults with KOA + insomnia, at least compared to those with KOA only. Increasing RAR robustness may mitigate this risk. Second, research comparing individuals with rheumatoid arthritis in Northern vs. Southern European climates suggest that rheumatoid arthritis may be aggravated by circadian rhythm abnormalities resulting from reduced light exposure (Cutolo, Villaggio et al., 2005). An intriguing question is whether KOA symptoms in older adults—and particularly those with insomnia—might be reduced by bright-light exposure or other chronotherapies. As mentioned above, interventions targeting RARs have been used to treat insomnia (Czeisler, Richardson et al., 1981).

This study's strengths include a sample of middle-aged and older adults with and without well-characterized KOA and/or chronic insomnia and objective measurement of RARs using one week or more of actigraphy data. However, it also has limitations. For example, that we only found differences in the F -statistic may have been due to our sample size. While our KOA + insomnia group had 114 subjects, the other groups had 28 or 30. Studies in larger samples of these populations are needed to further investigate differences in their RARs. In addition, participants reported their height and weight; thus, calculated BMI may not be accurate. Further, not all of our participants completed two full weeks of wrist actigraphy. It is possible that differences in duration of monitoring led to bias in results. Finally, this was a cross-sectional investigation, impeding us from evaluating the direction of potential causal links among variables of interest. Prospective studies are needed to investigate the temporal order of associations—in particular, whether aberrant RARs precede and might promote KOA symptoms.

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Dr. Michael Smith holds an equity stake in BMED Technologies, which develops self-help materials for behavioral disorders, including insomnia.

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Table 1
 Characteristics of Participants ($M \pm SD$ or n (%)) With and Without Knee Osteoarthritis and/or Chronic Insomnia.

	Total sample	(0) Normal Sleep (no OA)	(1) KOA Only (normal sleep)	(2) Insomnia Only (no OA)	(3) KOA + Insomnia	<i>p</i> -value
	<i>N</i> = 200	<i>n</i> = 28	<i>n</i> = 28	<i>n</i> = 30	<i>n</i> = 114	
Age (years)	60.2 $\pm$ 9.3	57.6 $\pm$ 7.4	66.9 $\pm$ 10.2	58.9 $\pm$ 8.6	59.4 $\pm$ 9.0	0.001 (1>0.2,3)
BMI (kg/m ²)	29.4 $\pm$ 6.1	25.7 $\pm$ 4.6	28.9 $\pm$ 4.6	26.8 $\pm$ 5.1	31.1 $\pm$ 6.3	0.001 (3>0.2)
Sex						0.005
Male	58 (29.0)	11 (39.3)	15 (53.6)	6 (20.0)	26 (22.8)	
Female	142 (71.0)	17 (60.7)	13 (46.4)	24 (80.0)	88 (77.2)	
Ethnicity						0.089
Caucasian	120 (60.0)	19 (67.9)	21 (75.0)	15 (50.0)	65 (57.0)	
African American	73 (36.5)	7 (25.0)	6 (21.4)	14 (46.7)	46 (40.4)	
Other	7 (3.5)	2 (5.0)	1 (3.6)	1 (3.3)	3 (2.7)	
Education						0.137
No or Some High School	6 (3)	0 (0.0)	2 (7.1)	2 (6.6)	8 (7.0)	
High School Diploma	28 (14.0)	3 (10.7)	3 (10.7)	4 (13.3)	18 (15.8)	
Some College	49 (24.5)	6 (21.4)	4 (14.3)	7 (23.3)	32 (28.1)	
College Diploma+	110 (55.0)	19 (67.9)	19 (67.9)	17 (56.7)	55 (48.3)	
Marital Status						0.798
Married/Living with Partner	93 (46.0)	11 (41.3)	15 (53.6)	14 (46.7)	52 (45.6)	
Single	39 (19.5)	8 (28.6)	4 (14.3)	8 (26.7)	19 (16.7)	
Separated/Divorced	62 (31.0)	8 (28.5)	6 (21.4)	8 (26.7)	40 (35.1)	
Widowed	6 (3.0)	1 (3.6)	3 (10.7)	0 (0.0)	2 (1.8)	
Employment Status						0.635
Employed (full- or part-time)	90 (45.0)	15 (53.5)	11 (39.3)	16 (53.3)	48 (42.1)	
Retired/Homemaker	76 (38.0)	7 (25.0)	17 (60.7)	10 (33.3)	42 (36.9)	
Unemployed	32 (16.0)	5 (17.9)	0 (0.0)	4 (13.3)	23 (20.2)	

	Total sample	(0) Normal Sleep (no OA)	(1) KOA Only (normal sleep)	(2) Insomnia Only (no OA)	(3) KOA + Insomnia	
	<i>N</i> = 200	<i>n</i> = 28	<i>n</i> = 28	<i>n</i> = 30	<i>n</i> = 114	<i>p</i> -value
Insomnia Severity Index	12.9 ± 8.2	1.4 ± 1.8	2.1 ± 2.6	17.6 ± 5.1	17.1 ± 4.8	<0.001 (3,2>1,0)
Apnea-Hypopnea Index	5.0 ± 4.2	4.5 ± 3.5	5.1 ± 3.7	4.6 ± 3.9	5.2 ± 4.6	0.802
CES-D	11.0 ± 8.8	3.1 ± 3.4	3.6 ± 4.3	13.9 ± 8.2	14.0 ± 8.4	<0.001 (3,2>1,0)
Clinical Pain (visual analog scale)	36.1 ± 21.1	13.4 ± 9.1	30.4 ± 18.8	18.1 ± 12.5	45.5 ± 18.5	<0.001 (3>1>0,2)

Abbreviations: BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale.

Table 2
Circadian Activity Rhythms (mean $\pm$ standard deviation) Across Participants Groups.

	Total sample	(0) Control Group	(1) KOA Only	(2) Insomnia Only	(3) KOA + Insomnia	
	<i>N</i> = 200	<i>n</i> = 28	<i>n</i> = 28	<i>n</i> = 30	<i>n</i> = 114	<i>p</i> -value [‡]
Amplitude	1.87 $\pm$.33	1.89 $\pm$ 0.34	1.97 $\pm$ 0.33	1.81 $\pm$ 0.33	1.87 $\pm$ 0.33	0.259
Acrophase (hr)	15.03 $\pm$ 1.21	15.21 $\pm$ 1.07	15.10 $\pm$ 0.93	14.70 $\pm$ 1.31	15.06 $\pm$ 1.27	0.390
MESOR	1.16 $\pm$ 0.20	1.15 $\pm$ 0.16	1.14 $\pm$ 0.17	1.13 $\pm$ 0.17	1.18 $\pm$ 0.22	0.656
F-statistic	3860.25 $\pm$ 2799.19	4549.80 $\pm$ 3206.31	5112.18 $\pm$ 4152.25	3790.66 $\pm$ 2165.16	3401.70 $\pm$ 2302.20	0.015 (1>3)

Note: MESOR = midline estimating statistic of rhythm

[‡] *p* value from omnibus MANOVA. Omnibus *p* (Wilks' Lambda) = 0.123

Table 3

Hierarchical Regression with *F*-statistic as Dependent Variable in Subsample with KOA only or KOA + insomnia (n = 140).

Predictors	Unstandardized B (SE)	t (DF)	p-value	Total R ² (R ² Change)
<i>Step 1</i>				.06
Group (KOA + insomnia vs. KOA only)	−1708.31 (585.63)	−2.92 (139)	.004	
<i>Step 2</i>				.09 (.04)
Age	35.11 (24.95)	1.41 (139)	.16	
Race	1039.44 (477.20)	2.18 (139)	.03	
Sex	988.89 (527.40)	1.88	.06	
Group (KOA + insomnia vs. KOA only)	−1560.19 (624.17)	−2.50 (139)	.01	
<i>Step 3</i>				.12 (.03)
CES-D score	−49.60 (30.04)	−1.65 (139)	.10	
Clinical Pain (visual analog scale)	−11.99 (12.95)	−.93 (139)	.36	
BMI	−57.94 (41.22)	−1.41 (139)	.16	
Age	21.68 (25.38)	.85 (139)	.40	
Race	870.76 (480.28)	1.81 (139)	.07	
Sex	1255.75 (536.79)	2.34	.02	
Group (KOA + insomnia vs. KOA only)	−945.60 (685.54)	−1.38 (139)	.17	

BMI = body mass index; CES-D = Center for Epidemiologic Studies Depression Scale.