Bone Reports 7 (2017) 156–163

Contents lists available at ScienceDirect

Bone Reports

journal homepage: www.elsevier.com/locate/bonr

Rest-activity circadian rhythms and bone mineral density in elderly men

Tara S. Rogers[a,*], Stephanie Harrison[b], Christine Swanson[c], Jane A. Cauley[d], Elizabeth Barrett-Connor[e], Eric Orwoll[f], Katie L. Stone[b], Nancy E. Lane[a], for the Osteoporotic Fractures in Men (MrOS) Study Research Group

[a] Center for Musculoskeletal Health, University of California, Davis Medical Center, 4625 2nd Avenue, Suite 2000, Sacramento, CA 95817, USA
[b] California Pacific Medical Center Research Institute, Mission Hall, 550 16th Street, San Francisco, CA 94158, USA
[c] Division of Endocrinology, Metabolism and Diabetes, University of Colorado Anschutz Medical Campus, 12801 East 17th Avenue, Mail Stop 8106, Aurora, CO 80045, USA
[d] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 130 DeSoto Street, Pittsburgh, PA 15261, USA
[e] Department of Family and Preventive Medicine, University of California, San Diego, 9500 Gilman Drive, #0607, La Jolla, CA 92093, USA
[f] Oregon Health & Science University (CR113), 3181 SW Sam Jackson Park Road, Portland, OR 97239, USA

ARTICLE INFO

Keywords:
Circadian
Rest-activity rhythm
Actigraphy
Pseudo F-statistic
Alpha statistic
Areal BMD

ABSTRACT

Background: Disrupted rest-activity circadian rhythm (RAR) patterns have been associated with poor health outcomes (i.e. diminished cognitive function, increased risk of dementia and falls). Circadian time cues in bone influence the differentiation of osteoblasts and osteoclasts, and bone turnover markers exhibit circadian variation; relationships between bone outcomes and RAR are emerging areas of research. We evaluated associations between RAR and areal bone mineral density (aBMD) at the total hip and femoral neck in older men from the Osteoporotic Fractures in Men (MrOS) cohort. We hypothesized that weaker RAR patterns would be associated with lower aBMD.

Methods: MrOS is an ongoing prospective cohort study following ambulatory men ≥ 65 years (n = 5994) at 6 U.S. clinics (baseline enrollment 3/2000–4/2002); participants for this analysis are from an ancillary study, Outcomes of Sleep Disorders in Older Men (MrOS Sleep). We included data from men who had technically adequate measures of RAR and aBMD at Sleep Visit 1 (12/2003–3/2005), with repeat aBMD at core Visit 3 (3/2007–3/2009) (n = 2412; mean age at Sleep Visit 1: 75.7 ± 5.2 years). aBMD was measured by dual energy x-ray absorptiometry (DXA). Actigraphs worn on the non-dominant wrist were used to collect circadian activity data over 4.8 ± 0.8 consecutive 24-hour periods. An extension of the traditional cosine curve was used to fit RAR to the activity data [Ancoli-Israel et al., 2003; Marler et al., 2006]. Six RAR parameters were evaluated: acrophase (time of peak activity), amplitude (rhythm strength), mesor (mean of activity fitted curve), pseudo F-statistic (overall circadian rhythmicity of rest and activity), alpha statistic (daytime to nighttime activity ratio), and beta statistic (daytime activity). Associations between RAR and aBMD (Sleep Visit 1), and RAR and ΔaBMD (Sleep Visit 1-Visit 3) were assessed with generalized linear models. Covariates included age, clinic site, physical activity, race, comorbidity, body mass index (BMI), smoking, alcohol, caffeine, beta blocker use, serum 25(OH) vitamin D and urinary melatonin and calcium.

Results: Pseudo F-statistic was significantly associated with total hip aBMD (p-trend = 0.009), femoral neck aBMD (p-trend = 0.007) and total hip ΔaBMD (p-trend = 0.017) in minimally adjusted models but not after multivariate (MV) adjustment. Alpha statistic was significantly associated with femoral neck aBMD (p-trend = 0.029) and femoral neck ΔaBMD (p-trend = 0.019) in minimally adjusted models; significance was retained in the femoral neck ΔaBMD model (p-trend = 0.034) after MV adjustment. There were no consistent, significant associations between the other RAR variables and aBMD or ΔaBMD.

Conclusions: The data demonstrate modest associations between overall circadian rhythmicity of rest and activity (measured by pseudo F-statistic), as well as daytime to nighttime activity ratio (measured by alpha statistic), aBMD and ΔaBMD, but adjustment for covariates related to lifestyle, BMI and comorbidities attenuated

Abbreviations: aMT6s, 6-sulfatoxymelatonin; BMD, bone mineral density; MrOS, Osteoporotic Fractures in Men prospective cohort study; MrOS Sleep, Outcomes of Sleep Disorders in Men, a MrOS ancillary study; PASE, Physical Activity Scale for the Elderly; RAR, rest-activity circadian rhythm; TST, total sleep time

* Corresponding author at: Center for Musculoskeletal Health, University of California, Davis Medical Center, USA.
E-mail addresses: tsrogers@ucdavis.edu (T.S. Rogers), SLitwack@psg.ucsf.edu (S. Harrison), CHRISTINE.SWANSON@ucdenver.edu (C. Swanson), jcauley@edc.pitt.edu (J.A. Cauley), ebarrettconnor@ucsd.edu (E. Barrett-Connor), orwoll@ohsu.edu (E. Orwoll), KStone@psg.ucsf.edu (K.L. Stone), nelane@ucdavis.edu (N.E. Lane).

https://doi.org/10.1016/j.bonr.2017.11.001
Received 20 June 2017; Received in revised form 25 October 2017; Accepted 7 November 2017
Available online 10 November 2017

most of these associations. These results suggest that RAR patterns are not independently associated with aBMD or four-year ΔaBMD at the total hip or femoral neck in older men, but additional research is needed.

1. Introduction

Increasing evidence suggests possible relationships between sleep, circadian rhythms and bone health in older men and women, related in part to the presence of circadian clock genes in bone cells, as well as melatonin (Albayrak et al., 2016; Cunningham and Di Pace, 2015; Stone et al., 2006; Stone et al., 2014; Swanson et al., 2015; Dudek and Meng, 2014; Amstrup et al., 2013). Circadian rhythm influences sleep and wakefulness (Saper et al., 2005; Dijk and Lockley, 2002), and rest-activity circadian rhythm (RAR) patterns can be measured with wrist-worn actigraphs; data can be fitted on a cosine curve for analysis (Martin and Hakim, 2011; Ancoli-Israel et al., 2003). We recently reported that later acrophase was associated with a modestly greater risk of falls in a cohort of elderly men enrolled in the Osteoporotic Fractures in Men (MrOS) prospective cohort study (Rogers et al., 2017). Common RAR measures include acrophase (time of peak activity level), amplitude (strength of rhythm), mesor (mean of activity fitted curve), pseudo F-statistic (a measure of overall circadian rhythmicity), alpha statistic (a ratio of daytime to nighttime activity), and beta statistic (a measure of daytime activity) (Paudel et al., 2010).

To further elucidate potential relationships between circadian rhythm and bone, we examined associations between RAR patterns and areal bone mineral density (aBMD) at the total hip and femoral neck. By utilizing data from MrOS and the MrOS ancillary study, Outcomes of Sleep Disorders in Men (MrOS Sleep), we had the opportunity to examine aBMD and RAR patterns cross-sectionally and longitudinally in a large cohort of community-dwelling older men. Participants were well-characterized for the RAR and aBMD variables, as well as confounding factors such as lifestyle habits, body composition and comorbidities.

Based on the previous associations between disrupted RAR patterns and deleterious health outcomes in the elderly (Paudel et al., 2010; Tranah et al., 2010; Tranah et al., 2011; Paudel et al., 2011; Rogers et al., 2017), we hypothesized that dysregulated RAR patterns would be associated with lower aBMD at MrOS Sleep Visit 1 and with greater aBMD loss over four years (MrOS Sleep Visit 1- MrOS Visit 3) in older men in the MrOs cohort.

2. Materials and methods

2.1. Study participants

The Osteoporotic Fractures in Men (MrOS) prospective cohort study follows ambulatory men ≥ 65 years of age (n = 5994) at six U.S. clinics (Birmingham, Alabama; Minneapolis, Minnesota; Palo Alto, California; Pittsburgh, Pennsylvania; Portland, Oregon; and San Diego, California). Enrollment in MrOS took place from March 2000 through April 2002, at which time men had to be 65 years of age or older. Exclusion criteria included the inability to walk without assistance and history of bilateral hip replacement (Orwoll et al., 2005; Blank et al., 2005). The MrOS Sleep ancillary study focuses on sleep disorders in older men; 3135 men (of the 5994 MrOS participants) were enrolled (105% of recruitment goal), for MrOS Sleep Visit 1 from December 2003 through March 2005. For the present study, we included data from men with technically adequate measures of RAR patterns and aBMD measurements at MrOS Sleep Visit 1 and aBMD at MrOS Visit 3 (March 2007–March 2009); the final sample size was 2412 (Fig. 1).

The study was approved by the Institutional Review Board at each clinic site, and all participants provided written informed consent.

2.2. Assessment of aBMD

Areal bone mineral density (aBMD, g/cm^2) of the total hip and femoral neck was measured by dual energy x-ray absorptiometry (DXA) (QDR 4500 W; Hologic Inc., Bedford, MA) at both visits.

2.3. Assessment of rest-activity patterns

Activity count data were collected from participants over 4.8 ± 0.8 consecutive 24-hour periods using wrist-worn actigraphy (SleepWatch-O; Ambulatory Monitoring, Inc., Ardsley, New York, USA). This time period met the minimum three day requirement for actigraphy monitoring according to the Centers for Medicare Services (CMS) (American Academy of Sleep Medicine, 2014). Participants wore the actigraph on the non-dominant wrist, and they were instructed to wear the actigraph at all times unless performing activities that would submerge it in

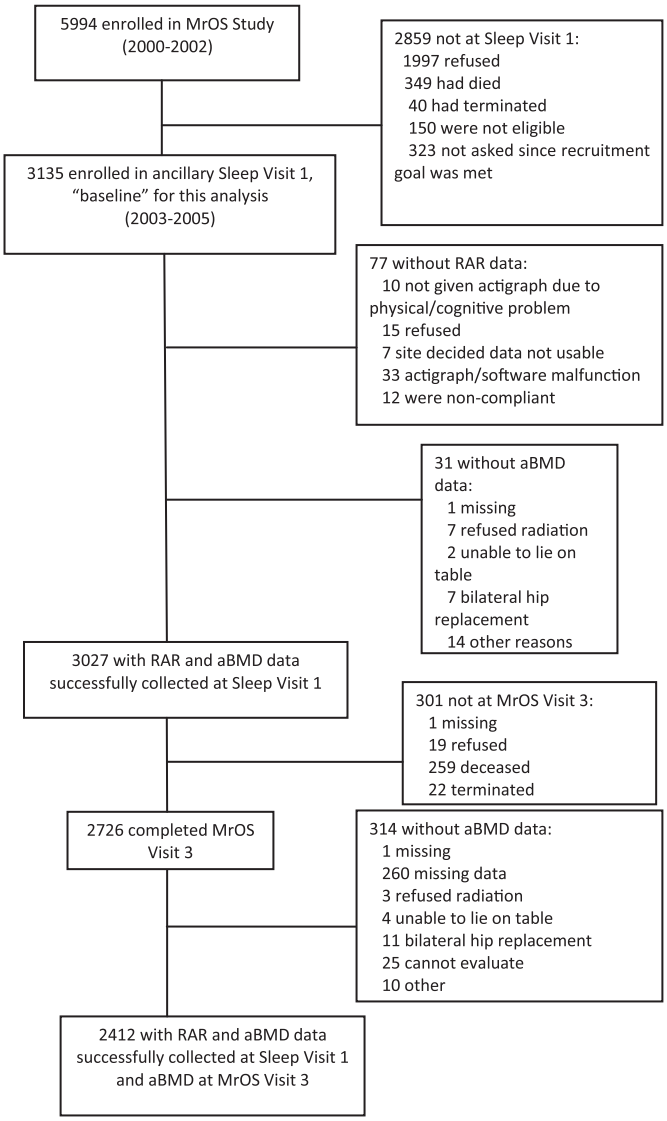

Fig. 1. Flow diagram of participant recruitment and inclusion. aBMD, areal bone mineral density. RAR, rest-activity circadian rhythm. MrOS, Osteoporotic Fractures in Men prospective cohort study.