Sleep Problems are Associated with Development and Progression of Lower Urinary Tract Symptoms: Results from REDUCE

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Abbreviations and Acronyms

BACH = Boston Area Community Health

BMI = body mass index

BPH = benign prostatic hyperplasia

CAMUS = Complementary and Alternative Medicine for Urological Symptoms

DRE = digital rectal examination

I-PSS = International Prostate Symptom Score

LUTS = lower urinary tract symptoms

MOS-Sleep = Medical Outcomes Study Sleep Scale

PSA = prostate specific antigen

REDUCE = Reduction by Dutasteride of Prostate Cancer Events

SCN = suprachiasmatic nucleus

Purpose: Although lower urinary tract symptoms and sleep problems often develop together, to our knowledge it is unknown whether sleep disturbances are linked to lower urinary tract symptoms development and progression. As measured by the 6-item MOS-Sleep (Medical Outcomes Study Sleep Scale) survey we examined the relationship between sleep problems, and the development and progression of lower urinary tract symptoms in the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) study.

Materials and Methods: REDUCE was a randomized trial testing prostate cancer chemoprevention with dutasteride in men with prostate specific antigen 2.5 to 10 ng/ml and a negative biopsy. At baseline men completed MOS-Sleep and a scaled average was used to calculate the sleep score. Men were followed for 4 years and I-PSS (International Prostate Symptom Score) was completed at baseline and every 6 months. Asymptomatic men had I-PSS less than 8 while symptomatic men had I-PSS 8 or greater. In the placebo arm of 2,588 men not receiving α-blockers or 5α-reductase inhibitors at baseline we tested the association between sleep problems and lower urinary tract symptom development and progression using Cox models.

Results: During followup lower urinary tract symptoms developed in 209 of 1,452 asymptomatic men (14%) and 580 of 1,136 (51%) with lower urinary tract symptoms demonstrated progression. On multivariable analysis higher sleep scores were suggestively associated with increased lower urinary tract symptoms in asymptomatic men (quartile 4 vs 1 HR 1.41, 95% CI 0.92–2.17, p = 0.12) and with lower urinary tract symptom progression in symptomatic men (per 10 points of sleep score HR 1.06, 95% CI 1.01–1.12, p = 0.029).

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Conclusions: Among men with lower urinary tract symptoms worse sleep scores were associated with the progression of lower urinary tract symptoms and among asymptomatic men worse sleep scores were suggestively associated with the development of lower urinary tract symptoms. If confirmed, these data suggest that sleep problems may precede such symptoms. Whether treating sleep problems would improve lower urinary tract symptoms requires further testing.

Key Words: prostate, prostatic hyperplasia, lower urinary tract symptoms, sleep, patient reported outcome measures

AMONG patients with LUTS nocturia is a common complaint.[1] Sleep disturbances associated with nocturia may worsen not only sleep quality but also quality of life.[2,3] Additionally, the effects of sleep disturbance could have long-lasting consequences, including increased type 2 diabetes and cardiovascular disease.[4] Despite the common co-development of LUTS and sleep problems, the relationship between the 2 conditions remains unclear.

The CAMUS trial examined the relationship between sleep problems and LUTS in men with preexisting LUTS.[5] This randomized North American trial compared saw palmetto extract vs placebo for LUTS in men with moderate to severe LUTS during 72 weeks and showed that saw palmetto was ineffective. A secondary analysis in 366 men examined baseline LUTS and sleep disturbance.[6] Sleep disturbance was quantified by a 4-item Jenkins sleep scale, which assesses trouble falling asleep and staying asleep, waking up several times per night and waking up tired. Higher Jenkins scores, indicating more sleep disturbance, were associated with worse baseline LUTS.[7] Another study in 339 participants from CAMUS showed a positive association between improved sleep and improved LUTS.[8] LUTS improvement was more strongly associated with improved sleep than nocturia. However, these studies were limited in sample size, were done for only 72 weeks and only included men with LUTS in North America.

BACH was an observational, longitudinal study of urological symptoms in 1,610 men and 2,534 women who completed data on LUTS and sleep quality, sleep restriction and sleep medications.[9] Sleep symptoms and LUTS were assessed at baseline and 5 years. Outcomes included the development of incident LUTS in men with sleep problems but no baseline LUTS and the development of incident sleep problems in men with LUTS but no baseline sleep problems. Individuals with baseline sleep problems but no LUTS were more likely to experience LUTS at 5 years. However, baseline LUTS was not associated with the development of sleep problems. Study limitations included the lack of clinical measures (PSA and prostate volume in men), absent interim measurements between baseline and 5 years, men and women as participants (if the goal was to analyze LUTS related to BPH) and a lack of information regarding worsening LUTS in those with baseline LUTS.

While CAMUS elucidated the significance of LUTS improvement in men with improved sleep habits and BACH highlighted LUTS development, there is a lack of consolidation of findings. As to our knowledge no prior studies have combined the analysis of LUTS development, LUTS progression and sleep disturbance, we used the REDUCE study to address this gap. We performed a post hoc analysis of REDUCE, a prospective, randomized trial of dutasteride vs placebo for prostate cancer prevention in men with elevated PSA and negative biopsy. Men were administered the 6-item MOS-Sleep survey[10] at baseline to assess sleep and they were followed every 6 months to monitor LUTS. Based on CAMUS and BACH results, we hypothesized that men with higher baseline sleep problems would be at higher risk for LUTS than those without LUTS and greater LUTS progression than those with LUTS.

METHODS

Study Cohort

The REDUCE study design was previously described.[11] The study was approved by the institutional review board at each site and all participants provided informed consent. The men were 50 to 75 years old. PSA was 2.5 to 10.0 ng/ml in those 50 to 60 years old and 3.0 to 10.0 ng/ml in those 61 to 75 years old. These men also had a negative 6 to 12 core prostate biopsy within 6 months of study enrollment, prostate volume less than 80 ml, no prior prostate surgery or prostate cancer diagnosis and I-PSS less than 25 or less than 20 if on α-blockers.[12,13] Men were excluded from analysis if they had a history of prostate cancer, high grade intraepithelial neoplasia or atypical small acinar proliferation. A total of 8,122 men were randomized to receive placebo or dutasteride 0.5 mg per day.

In this post hoc analysis we limited our analysis to 4,063 men in the placebo arm. We excluded from study 266 men with missing MOS-Sleep data at baseline, 184 missing covariates for multivariable analysis, 725 who received α-blockers or 5α-reductase inhibitors at baseline,