2013

Altered circadian rhythms and sleep in aging and sex as factors in nocturia

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http://hdl.handle.net/2144/12181

Boston University
BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

ALTERED CIRCADIAN RHYTHMS AND SLEEP IN AGING AND SEX AS FACTORS IN NOCTURIA

by

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B.A., University of Illinois, 2011

Submitted in partial fulfillment of the requirements for the degree of

Master of Arts

2013
ACKNOWLEDGEMENTS

I would like to express my deep gratitude to Dr. Jeanne F. Duffy, my research supervisor and mentor, for her patient guidance, encouragement and useful critiques of this research work. She has kept me on track and always held me to high standards, helping me to truly appreciate clinical research.

I would also like to thank Dr. R.J. Rushmore for his understanding, helpful advice, and earnest interest in my research. His humor and amiability comforted me when I was overwhelmed by this endeavor.

My grateful thanks are also extended to Dr. Kevin Loughlin for agreeing to collaborate on the questionnaire studies and Mike Meyers for helping collect the questionnaire data. Finally, I wish to thank Dr. Chang G. Park for his help in doing the statistical analysis.
ALTERED CIRCADIAN RHYTHMS AND SLEEP IN AGING AND SEX AS FACTORS IN NOCTURIA

HONGCHAI PARK

Boston University School of Medicine, 2013

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ABSTRACT

Background: Nocturia is one of the most common causes of sleep disruption and of reduced quality of life. This nocturnal tendency to void increases with age, and is reported to affect men more than women. The underlying causes of these age- and sex-related differences have been inconsistently explained in literature. There are age-related changes in sleep architecture and in the day-night rhythm of urine output, but how each of these changes influence nocturnal voiding is unclear. Furthermore, sex-related differences sleep architecture are not well linked to nocturia.

Diminished urine output is achieved through urine concentration either via water reabsorption or sodium retention. There is a day-night variation in urine output in humans, with nighttime output in healthy young adults representing about 25% of total 24-hour production. A variety of hormones play a role in fluid and sodium balance, including vasopressin, atrial natriuretic peptide, and the renin-angiotensin-aldosterone system. Several of these hormones have been reported to show day-night variations, but
whether these represent circadian rhythms or effects of day-night changes in behavior is not clear. Without understanding how diuretic and anti-diuretic hormones vary across day and night, their role in nocturia remains unclear. Furthermore, if changes in the amplitude of the circadian rhythm of such hormones occur with age, it represents a potential novel mechanism contributing to nocturia, and a potential therapeutic target.

Methods: We conducted two studies to investigate the connection between nocturia and age- and sex-related changes in sleep and circadian rhythms. In the first study, four questionnaires were given to 291 older adults, 204 males and 87 females. The questionnaires asked about sleep quality, daytime sleepiness, urological complaints, and general napping and medications. Questionnaire responses were compared between the men and women to determine if there were sex-related differences in sleep and urological complaints. To investigate associations between urological complaints and sleep complaints, the responses on the questionnaires were also compared within each group.

The second study consisted of ten healthy young adults and nine healthy older adults who each took part in a multi-day inpatient circadian rhythm study. That study included a constant routine (CR) circadian phase and amplitude assessment during which activity, posture, sleep-wake state, room environment, and food and fluid intake were controlled throughout day and night. Blood samples for hormone analysis were collected every 4 hours throughout the CR and assayed after the study was complete for aldosterone, atrial natriuretic peptide, and vasopressin using a radioimmunometric assay. The data from the participants in each age group were averaged and cosinor analysis was
used to determine whether there was significant circadian rhythmicity in the hormone data, and if so whether the hormone timing and amplitude differed between the two age groups.

Results: In the questionnaire study, there was a positive correlation between sleep complaints and urological complaints in women. In men, there was a positive correlation between sleep complaints and daytime sleepiness, daytime sleepiness and urological complaints, and sleep complaints and urological complaints.

In the hormone study, there was a significant circadian variation in aldosterone for young subjects (but not older subjects), and the waveform was well-described by a cosine model. None of the other hormones exhibited a significant circadian variation in either age group.

Conclusion: In the questionnaire study, we found that poorer sleep quality was associated with more urological complaints in both women and men. In men, daytime sleepiness was also correlated with urological complaints, and decreased quality of sleep was correlated with increased daytime sleepiness.

In the hormone study, we found evidence for a sleep-independent increase in aldosterone levels at night, suggestive of an underlying rhythm in aldosterone secretion. This circadian rhythm in aldosterone secretion may contribute to the circadian rhythm in urine production, and further studies are required to determine whether a change in the amplitude of this rhythm with aging is associated with nocturia.
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INTRODUCTION

Nocturia

The International Continence Society defines nocturia as waking one or more times at night to void, while more recently the American Urological Association has defined it as the need to urinate at least twice during the night (Abrams et al., 2002; Brawer et al., 2007). Traditionally, voiding during the night was attributed to benign prostate hypertrophy (BPH), a problem only found in males (Weiss, Blaivas, Stember, & Brooks, 1998). Yet surgical therapy of these obstructions have been found to be generally ineffective (Alternate methods in the treatment of benign prostatic hyperlasia, 1993). The traditional beliefs of nocturia have become obsolete as more studies are being done on this condition. Defining the need to void at night has been useful for determining its impact as a symptom of various disorders and diseases (Levkowicz, Whitmore, & Muller, 2011). It is now well-known that nocturia is a multifactorial condition, from nocturnal polyuria and detrusor over-activity to uncompensated heart disease and estrogen deficiency (Weiss & Blaivas, 2000).

Weiss et al. have proposed a classification of a system to better identify the etiology of nocturia and the appropriate treatment (Weiss et al., 1998). As the definitions have varied, it has been difficult to measure the prevalence of nocturia, but it is well-established that complaints of voiding at night are not limited to men (Wein, Lose, & Fonda, 2002). Weiss et al. has described three general pathophysiology for nocturia: 1) decreased nocturnal bladder capacity; 2) nocturnal polyuria; or 3) a combination of the two. Daytime polyuria, or having a 24-hour urine output greater than 2500 mL may be
responsible for an increased urine production, but is classified separately (Weiss et al., 1998). Nocturnal polyuria is an increased urinary output during the night of 35% or more of the normal 24-hour urine production (Asplund, 1995; Weiss, Blaivas, Stember, & Chaikin, 1999). Some causes of nocturnal polyuria include congestive heart failure, sleep apnea, or excess fluid intake before bedtime (“Nocturia,” 2009). Diminished nocturnal bladder capacity occurs when the volume voided at night is less than the functional bladder capacity (the maximum volume of void) (Abrams, Blaivas, Stanton, & Andersen, 1988). Some causes of low nocturnal bladder capacity include bladder obstruction, bladder inflammation, or benign prostatic hyperplasia (“Nocturia,” 2009). The multifactorial etiology of nocturia is becoming more recognized. The standardization committee of International Continence Society has further defined various terms of nocturia so that different medical specialties could more clearly communicate about this common symptom, and have helped identify ways to treat the different causes of nocturia (Abrams et al., 2002).

To fully determine the etiology of nocturia, an evaluation beyond the bladder should be done. A general physical examination may include assessing genitourinary health, checking for bladder distension, and evaluating for autonomic neuropathy (T. Johnson, 2013). Laboratory tests may include fluid or electrolyte assessment, urinalysis, bladder ultrasound, tissue cultures, and polysomnograms. The standardization subcommittee of the International Continence Society recommends keeping a frequency-volume chart to help clinicians distinguish between the three etiologies of nocturia (Abrams et al., 2002). This chart is a diary for patients to record the number, volume, and
timing of voids over 24 hours in order to calculate various indices in guiding the
differential diagnosis of nocturia (Weiss et al., 1998, 1999). It is important to determine
the underlying cause of nocturia to most effectively treat the condition with the
appropriate intervention and medication.

**Characteristics of Sleep**

Sleep is well recognized but not thoroughly understood. This mysterious
unconscious state is a time when the body can recover and consolidate memory, and has
many detrimental effects on health when sleep needs aren’t met, such as lowering life
expectancy and decreasing cardiovascular health (Sejnowski & Destexhe, 2000). The
ubiquity of sleep has made sleep and wakefulness a well-documented behavior found to
be conserved throughout evolution (Campbell & Tobler, 1984). Based on scientific
observations, sleep has been characterized by: (1) a period of reduced activity, (2)
association with a typical posture, (3) decreased response to external stimuli, and (4) a
state relatively easy to reverse (‘‘The Characteristics of Sleep,’’ 2007).

Characteristics of wakefulness and sleep states were established through
monitoring the electrical activity of neurons with an electroencephalogram (EEG)
(William Dement & Kleitman, 1957; Loomis, Harvey, & Hobart, 1935). The
measurements identified differences in brainwave activity between sleep and wakefulness
and different neuronal firing patterns across a sleep episode.

In the 1950s and 60s, Kleitman and Aserinsky discovered regular alterations of
rapid eye movement (REM) and non-REM phases during sleep (Aserinsky & Kleitman,
1953). Vivid dreaming was correlated with REM sleep, demonstrating the active aspect of sleep. They also elucidated that REM sleep is characterized by a profound loss of skeletal muscle tone. The EEG pattern of REM sleep shows faster activity with distinctive saw-tooth waves (W Dement & Wolpert, 1958).

A typical 8-hour nighttime sleep episode in humans is made up of 4-5 sleep cycles (Münch, Cain, & Duffy, 2007). One sleep cycle lasts for about 90-100 minutes, and consists of the two distinct stages of REM and non-REM (NREM) sleep. There is a longer REM and NREM Stage 2 for the later part of the sleep. The sleep structure can be seen in Figure 1. Brain waves decrease in frequency and increase in amplitude on the recordings of EEG as wakefulness transitions to sleep (Figure 2). This increase in amplitude is a reflection of the rising synchronization of cortical neurons. These EEG recordings are used to divide the NREM part of sleep into 3 or 4 stages (Carskadon & Dement, 2011). Stage 1 is the transitional stage between the wake and sleep states and thus has some alpha waves and low-voltage waves. Alpha waves are characteristic of relaxed wakefulness with a range of 8-12 Hz. Stage 2 gets longer after each cycle and has low-voltage waves. Sleep spindles and K-complexes are mixed-frequencies that are characteristic of Stage 2. Stages 3 and 4 are known as “slow-wave sleep” (SWS), or deep sleep, which is found mostly during the one or two sleep cycles. SWS is defined by containing more than 20% delta waves (Münch et al., 2007). Delta waves have relatively large amplitudes and low frequency (1-3 Hz) and are a result of the synchronization of rhythmic thalamocortical activity (Steriade, McCormick, & Sejnowski, 1993).
Figure 1 – Representation of the Human Sleep Architecture. REM sleep becomes progressively longer across the night and NREM contains less slow-wave sleep (Stage 3/4) across the night. Figure from (Carskadon & Dement, 2011).
Figure 2 – EEG Wave Recordings During Different Brain States. A – Alpha waves during quiet wakefulness. B – Stage 1 Sleep. C, D – Stage 2 Sleep. E – Slow-wave sleep during Stages 3 and 4. F – REM sleep. Figure adapted from (Münch et al., 2007).
Sleep Regulation

Sleep is the result of two interacting regulatory mechanisms, homeostatic drive and circadian rhythmicity. Sleep homeostasis is essentially a sleep drive that increases during wakefulness and dissipates during sleep (Borbély & Achermann, 1999). One hypothesis suggests that the build-up of adenosine in the brain, a by-product of energy consumption, promotes sleep drive (Blanco-Centurion et al., 2006). Any change in the accumulation of sleep will change the sleep pressure accordingly. The physiological drive for sleep pressure is found to be measured by sleep EEG slow waves (D. J. Dijk, Brunner, Beersma, & Borbély, 1990).

The circadian process is a 24 hour rhythm of sleep propensity through physiological activity (Münch et al., 2007). This includes many neuronal and hormonal influence on the biological clock where the drive to sleep is stronger at some points and weaker at others within the 24-hour day. A healthy individual on a normal day shift work schedule would not have problems going to sleep at night because the sleep pressure building up during the day is in phase with sleep cycle of the internal circadian rhythm which promotes sleep at night. The strongest sleep drives in the adult are typically between 2:00 to 4:00 am and 1:00 to 3:00 pm, but can vary widely (“Sleep Topics,” 2011). Naturally, there will be problems with sleep if the homeostatic sleep drive is strongest during the wake cycle of circadian rhythm. For example, a night shift worker staying up all night will be working as the internal circadian clock is promoting sleep, making it difficult to remain awake. Although the homeostatic drive to sleep continues to
build up, the night shift worker may then have trouble going to sleep during the daytime because the internal circadian clock is in its wake cycle.

**Human Circadian Rhythmicity**

Circadian rhythm is roughly a 24 hour cycle that helps us behave accordingly with the day and night cycle. It is ubiquitous in nature – from unicellular organisms to mammals (Czeisler et al., 1999). These daily oscillations are generated endogenously and are not solely the result of periodic changes in behavior (for example, sleep-wake) or the environment (for example, light-darkness). Therefore, a daily rhythm is not a true circadian rhythm unless the rhythm is demonstrated to persist in the absence of periodic changes in behavior and environmental cues. Therefore, when determining whether a rhythm is circadian, periodic zeitgebers (German for “time giver”) such as light-darkness, feeding-fasting, activity-rest, must be taken into account and controlled (Lack & Wright, 2007). In humans, these can be controlled in experiments with Constant Routines, where posture, lighting, and food/fluid intake are controlled for at least 24 hours to minimize their effects on circadian rhythms (Jeanne F Duffy & Dijk, 2002).

The suprachiasmatic nucleus (SCN) in humans is a cluster of neurons on the left and right side of the third ventricle that hosts the self-sustaining, central pacemaker of the biological clock (*Suprachiasmatic nucleus*, 1991). The main external synchronizer of the SCN is light. There are light-sensitive neurons in the retina that relay information of the external light/dark cycle from the environment to the SCN through the retinohypothalamic tract (RHT) (Takahashi, DeCoursey, Bauman, & Menaker, 1984).
Several studies found that blind subjects have free-running rhythms due to the absence of light entrainment (Sack, Brandes, Kendall, & Lewy, 2000; Sack, Lewy, Blood, Keith, & Nakagawa, 1992). Lockley et al. found that individuals with a particular blindness can entrain to day-night cycles, suggesting that there are specific light receptors (Lockley et al., 1997). In fact, the SCN can get light signals from the photoreceptors or melanopsin containing ganglion cells (Khamsi, 2005). When both of these are affected, the SCN cannot get light signals. While light is the dominant synchronizer of circadian rhythm, there are several potential non-photic zeitgebers in humans that may act under very specialized conditions, and they include exercise, timing of meals, and social cues (Mistlberger & Skene, 2005).

The information received at the SCN is sent to the pineal gland, where melatonin is synthesized and secreted (Arendt, 1995). Melatonin conveys the light/dark cycle throughout the body (Zhdanova & Tucci, 2003). It is described as the ‘hand’ of the clock, because the melatonin rhythm can indicate the phase of the SCN. Many other physiological processes receive timing information from the SCN.

**Circadian Rhythm and Sleep**

The circadian rhythm of sleep propensity plays a significant role in sleep architecture and timing in humans. The propensity to fall asleep appears to be determined by the circadian system with most rapid increase of sleep propensity after melatonin secretion begins and when core temp is falling (D.-J. Dijk & Lockley, 2002; Liu et al., 2000). The duration, timing, and subjective measures of sleep episodes all vary with
circadian phase. The amount of REM sleep varies significantly with the circadian rhythm measured by the 24 hour body temperature (Czeisler, Zimmerman, Ronda, Moore-Ede, & Weitzman, 1980). An analysis of 359 sleep-wake cycles have shown that the phase of circadian rhythm determines the duration of prior wake and sleep length (Strogatz, Kronauer, & Czeisler, 1986). In other words, the circadian processes influence the sleep length and wake time. There is also an assessment of somnolence by measuring sleep latency and presence of REM sleep throughout the day (Carskadon et al., 1986). Several measures of sleep quality decline when sleep and circadian phase are not synchronized in healthy adults (Campbell & Dawson, 1992). Synchronizing the timing of sleep with the circadian phase is important for both healthy and unhealthy subjects (Campbell, Dawson, & Anderson, 1993; Ozaki, Uchiyama, Shirakawa, & Okawa, 1996). Without the proper synchronization, the body is stressed by unsynchronized sleep pressures. Czeisler and Dijk have confirmed that the timing of endogenous circadian phase affects REM sleep, and revealed that the pacemaker consolidates sleep most effectively when in phase with the sleep episode (D. J. Dijk & Czeisler, 1994, 1995). The appropriate synchronization of the circadian pacemaker and the sleep-wake cycles is also critical for better alertness, performance, mood, and memory (Boivin et al., 1997; D. J. Dijk, Duffy, & Czeisler, 1992; M. P. Johnson et al., 1992).

**Age-related Changes in Sleep Regulation**

Age-related reduction in uninterrupted sleep is due to an increase in awakenings, an increased susceptibility to circadian phase misalignment, and the reduction of sleep
duration at all circadian phases (D. J. Dijk, Duffy, & Czeisler, 2001; D. J. Dijk, Duffy, Riel, Shanahan, & Czeisler, 1999; D. J. Dijk & Duffy, 1999; J F Duffy, Dijk, Klerman, & Czeisler, 1998). The circadian rhythm for older people allows for a smaller opportunity to consolidate their sleep. Dijk and Czeisler have revealed a relationship between circadian phase and the ability to maintain a high sleep efficiency in both young and older subjects (D. J. Dijk & Czeisler, 1994). Older subjects report more difficulty sleeping when sleep-wake episodes are improperly aligned with the endogenous rhythm (D. J. Dijk et al., 1999; D. J. Dijk & Duffy, 1999; M L Moline et al., 1992). Young adults are more likely to have uninterrupted sleep episodes of 7 to 9 hours than older adults (D. J. Dijk & Czeisler, 1995; D. J. Dijk et al., 2001, 1999; J F Duffy et al., 1998).

Age-related changes in sleep regulation are also present in the homeostatic process. Homeostatic sleep pressure can be measured by the EEG power density described as slow-wave activity (SWA), primarily measured in NREM sleep (Borbély, Baumann, Brandeis, Strauch, & Lehmann, 1981; Brunner, Dijk, Tobler, & Borbély, 1990). In general, slow-wave sleep is maximal in adolescents and continuously declines with age (Carskadon & Dement, 2011). The level of SWA increases with the time awake (Brunner et al., 1990; Dijk & Czeisler, 1993; D. J. Dijk, Brunner, Beersma, et al., 1990; D. J. Dijk, Brunner, & Borbély, 1990). A study using sleep deprivation reported that older people had a homeostatic drive for sleep that could not adequately maintain high sleep efficiency towards the end of the sleep episode (D. Dijk, Kelly, Riel, Duffy, & Czeisler, 1999). The difference of sleep homeostasis between young and older people was further elucidated in a study by Klerman and Dijk (Klerman & Dijk, 2004). In this
study, subjects were given 16 hour sleep opportunity per day for 3 days in the laboratory after 3 weeks of maintaining their habitual sleep behavior at home. The older group slept less during their sleep opportunity. These age-related changes in the homeostatic sleep process may contribute to the greater incidence of sleep disturbances.

Elderly people have weaker regulation of sleep and wakefulness (Cajochen, Münch, Knoblauch, Blatter, & Wirz-Justice, 2006). Younger adults spend about half as much time during the night in unwanted wakefulness than older adults (D L Bliwise, 1993). Many studies found that older people complained of involuntarily waking up early in the morning (D J Foley et al., 1995; Mant & Eyland, 1988; McGhie & Russell, 1962). Dijk et al. reported that the higher likelihood of awakening in the elderly is due to the age-related reduction in stages 3 and 4 of NREM sleep (D. J. Dijk et al., 2001). The deep sleep of stages 3 and 4 accounts for the difficulty to awaken an individual during these stages. The lightening of sleep homeostatic processes with age may be the cause of higher sensitivity to disturbances, such as sound or light, while asleep (Zepelin, McDonald, & Zammit, 1984). An internal source of awakening may be to empty the bladder at night. Voiding at night is reported to be a major cause of sleep disturbance affecting around half of the adults in a study across five countries (Irwin et al., 2006). These age-related changes in sleep homeostasis may contribute to the higher incidence of nocturnal voiding observed with aging (Donald L Bliwise et al., 2009). The bladder wall stretch receptors may more likely awaken older people because less of their sleep is spent in the deep slow-wave sleep. Any other internal or external stimulus may awaken older people due to the age-related changes in sleep depth and continuity. This greater tendency
to be awakened by stimuli from lighter sleep may lead older individuals to be conscious of a filled bladder and empty it. It is difficult to ascertain whether people awaken to void or realize they have to void after awakening. Older adults have weaker sleep regulation, although the underlying cause for age-related differences is not always clear.

**Sex Differences in Sleep Regulation**

Delta waves are found primarily during Stages 3 and 4 of NREM, which is also known as slow-wave sleep. In one study, women did not show the same significant decline in the amount of time spent in stages 3 and 4 of NREM as in men (Sheldon, Ferber, & Kryger, 2005). A cross-sectional analysis on over 2,600 participants measured the quality of sleep based on sex, ethnicity, and age (Redline et al., 2004). Sex was responsible for the largest variance within each measure of sleep architecture. Men spent significantly less time in stages 3 and 4 of NREM, more time in lighter sleep of stages 1 and 2, and have a higher likelihood of arousal at night. There is a general assumption that the differences in sleep between male and female arise after puberty (“Sleep, Sex Differences, and Women’s Health,” 2003).

One study reported that women had significantly shorter circadian period relative to the intrinsic rhythm of melatonin and core body temperature. (J. F. Duffy et al., 2011). Cain *et al.* found in their study that the timing of the core body temperature and melatonin secretion was earlier in young women despite having the same sleep timing as men (Cain *et al.*, 2010). Given that circadian rhythm and melatonin influence sleep
structure, these findings present important implications for understanding sex differences in sleep timing and duration.

Two studies reported women having higher baseline slow wave activity levels and a greater slow wave activity rebound after sleep deprivation (Armitage, Smith, Thompson, & Hoffman, 2001; Manber & Armitage, 1999). These differences between men and women in slow wave activity response may arise from a difference in the accumulation and dissipation of homeostatic sleep pressure. Several studies have shown that hormones affect properties of sleep, including spindle frequencies and slow wave activity (Dzaja et al., 2005; Margaret L Moline, Broch, Zak, & Gross, 2003; Shechter & Boivin, 2010). The hormonal changes in the lives of healthy women are more dynamic than in men, which may explain the sex differences in circadian rhythm and sleep. There is a lack of conclusive evidence that controls for the complex hormone interactions of the human body to accurately explain these differences between men and women.

**Urine Production and Output**

Urine is produced to eliminate waste from the body, and also to maintain balance and composition of extracellular fluid. Water and sodium balance are two factors that influence urinary output by the kidney. In the normal kidney, the urine output can be diminished by concentrating urine by water reabsorption or sodium retention.

Arginine vasopressin (AVP) is a water-conserving hormone that regulates body water retention. It is synthesized in the hypothalamus and released mainly when plasma osmolality increases. The target receptors for AVP are found in the distal tubules of the
kidney where it can influence urine concentration. AVP is released in response to environmental changes, which is characteristic of the reported diurnal rhythm by Rittig et al. (Rittig, Knudsen, Nørgaard, Pedersen, & Djurhuus, 1989). Their study showed that normal subjects had a significant increase in AVP levels during the night.

Atrial natriuretic peptide (ANP) is released by the heart to control fluid homeostasis in response to high blood pressure. The atria release ANP to stimulate sodium secretion, and subsequently fluid secretion by the kidney. ANP inhibits the release of AVP and suppresses the effect of the renin-angiotensin system, and thus aldosterone (Bold, 1985). This peptide’s inverse effect of the renin-angiotensin-aldosterone system (RAAS) makes it a likely component in nocturia. The rhythm of ANP secretion has not been agreed upon, making it difficult to assess the specific influences of this hormone on nocturia (Elias, Antunes-Rodrigues, & Moreira, 1997; Follenius, Brandenberger, & Saini, 1992; Rittig et al., 1991).

The renin-angiotensin-aldosterone system (RAAS) has a role in the conservation of sodium in the kidneys via the action of aldosterone (Boron, 2005). The kidney secretes renin when blood volume is low, which is converted into angiotensin I, then into angiotensin II. Angiotensin II promotes vasoconstriction and also stimulates the release of aldosterone. Aldosterone promotes sodium and water reabsorption in the kidney. The renin-angiotensin-aldosterone system has been shown to exhibit a diurnal rhythm. (Hurwitz, Cohen, & Williams, 2004). Renal sodium conservation is sensitive to environmental changes.
Overall, there are many hormones that affect urine output, and thus are important in understanding the etiology and treatment of nocturia.

**Day-night Variation of Urine Output**

Kirkland *et al.* reported that his young and elderly groups had similar 24 hour mean volumes of urine output, but the elderly group excreted more urine throughout the night than the young group (Kirkland, Lye, Levy, & Banerjee, 1983). Although the elderly group had approximately 30% less 24 hour sodium excretion than the young, they were still found to have a higher sodium excretion at night. Two other studies found that the elderly with nocturnal polyuria have almost twice as much of their 24 hour urine output at night relative to a control group (Hvistendahl, Frøkiaer, Nielsen, & Djurhuus, 2007; Robertson *et al*., 1999).

An earlier study revealed that posture plays a role in this day-night variation in urine output. In 1957, Thomas *et al.* showed that standing up from the recumbent position resulted in a decrease in urine, sodium, and chloride output, while the opposite was true for lying down (Thomas, 1957). They postulated that their findings are maintained by some hormonal mechanism. Gross later proved this to be the plasma renin angiotensin-aldosterone system (Gross, 1958). Cohen *et al.* demonstrated that plasma renin levels are affected by posture (Cohen, Conn, & Rovner, 1967). The upright posture leads to a drop in the renal arterial pressure at the juxtaglomerular apparatus. This stimulates the release of renin, and subsequently stimulates the release of aldosterone to induce water and sodium retention. Their data also demonstrated that the change in renin activity is due to
the changes in level of enzyme rather than of other components of the RAAS. It is therefore important to control for posture when investigating urine output.

Mills et al. conducted several studies in the 1970s to elucidate that the day-night variation in urine production is also influenced by an endogenous rhythm (Mills, Minors, & Waterhouse, 1978). In order to remove exogenous influences on a potential internal rhythm, food and fluid intake, posture, and lighting were all controlled for through a constant routine, while measuring urine production throughout the study. These measures were taken to distinguish a circadian rhythm from a diurnal rhythm. After controlling for exogenous influences, Mills et al. was able to show the circadian rhythmicity of urine output. Their findings indicated that urine output was the lowest at midnight, which supports Mills’ earlier work. This rhythm in urinary output was found to similar to that of vasopressin (George et al., 1975). A similar pattern was found in atrial natriuretic peptide, a hormone that is found to be at maximum levels at midnight (Rittig et al., 1991). Without taking the same measures as Mills et al., these two hormones were identified to exhibit a diurnal rhythm, although whether they exhibit a true circadian rhythm could not be determined from the experimental procedures used.

The day-night pattern of urine output plays an important role in nocturia. There is strong evidence for greater urine output at night among older people, and urine output is influenced by age, posture, and hormones. Each of these components should be considered when investigating nocturia.
Circadian Rhythm of Hormones Affecting Urine Output

A study that grouped subjects into four different conditions found that the circadian rhythm in urine output is sensitive to both internal and external stimuli (Minors & Waterhouse, 1982). A clear circadian rhythm in urine composition and volume is reported in young subjects (Kamperis et al., 2004; Kawasaki et al., 1990). The observed pattern of urine output is supported by the reported circadian rhythms of AVP, ANP, plasma renin activity (PRA), and aldosterone (Cugini et al., 1992a; Donckier, Anderson, Yeo, & Bloom, 1986; Maggioni, Lucini, Antinozzi, & Pagani, 2001; Mulrow & Ganong, 1961; Portaluppi et al., 1990; Rittig et al., 1991). However, most of these studies could not verify a clear circadian rhythm because they did not control for sleep, posture, and other factors. A study by the Brandenberger group included both sleep deprivation and sleep shifting (to the daytime), and concluded a close link between aldosterone secretion and the sleep-wake cycle, rather than a circadian rhythm in aldosterone secretion (Charloux, Gronfier, Lonsdorfer-Wolf, Piquard, & Brandenberger, 1999). They found that aldosterone levels were significantly higher during sleep whether sleep occurred during the day or night. A later study by the same group found that sleep deprivation inhibits the increase in aldosterone levels during nocturnal sleep (Charloux et al., 2001). The presence of circadian rhythmicity in hormones affecting urine output has clear implications for nocturnal voiding. If secretion of a hormone exhibits a circadian rhythm, the hormone levels will vary with the time of day and will vary independent of postural changes, sleep-wake behavior, or day-night differences in activity. If secretion of a hormone shows day-night (diurnal) differences that are not circadian, the hormone levels
will change based on the behavioral and/or environmental differences between day and night, but under conditions where day-night differences in behavior (posture, activity level, sleep-wake state) or environment (light-dark) are controlled will not show such variation. Most reported hormone rhythms have not been investigated closely enough to distinguish between diurnal and circadian rhythms. It is difficult to treat nocturia without understanding the secretion patterns of hormones affecting urine output.

**Age-related changes in AVP**

The diurnal rhythm of vasopressin is established during childhood, and nocturnal release becomes attenuated with age (Asplund & Aberg, 1991; Ouslander et al., 1998). The diurnal rhythm of vasopressin in young adults was found to be significantly higher at night (George et al., 1975). Several studies show that with age, the day and night time levels of vasopressin become similar due to the blunting or lack of nocturnal release (Asplund & Aberg, 1991; Forsling, Montgomery, Halpin, Windle, & Treacher, 1998; T. M. Johnson, Miller, Pillion, & Ouslander, 2003; Moon et al., 2004). Asplund found that the levels of vasopressin were similar in older subjects between those with and without nocturnal polyuria, suggesting that the underlying cause of nocturia may not directly be due to changes in AVP (Asplund, 2002). These age-related effects may be due to an inadequate renal tubular response to vasopressin (Miller, 2009). Higher urine output at night in older adults may be due to attenuation of AVP release or inadequate response to the hormone.
Age-related changes in ANP

Johnston et al. suggested that the lower renin levels associated with age may be influenced by the rise in ANP with age (Johnston et al., 1989). Cugini et al. investigated the effect of aging on circadian rhythm of hormones by controlling for posture, lighting, and food and fluid intake (Cugini et al., 1992b). The overall levels of ANP in the older subjects were significantly higher than the young subjects. However, they report that the ANP circadian rhythm is lost in the elderly while aldosterone and renin rhythms were still detected, suggesting that the inhibitory action of ANP might be lost with age. These results suggest that the age-related increase of plasma ANP concentration contributes to the higher urine output at night.

Age-related changes in the RAAS

There are many studies that show that the RAAS system goes through age-related changes. Healthy subjects 85 years of age displayed significantly lower levels of plasma renin and aldosterone concentrations than normal 40 year old subjects (Skøtt, Ingerslev, Damkjaer Nielsen, & Giese, 1987). Several studies reported an age-related decrease in mean levels of plasma renin activity (Belmin, Lévy, & Michel, 1994; Cugini et al., 1992b; Lall, Peshin, & Karmarkar, 1995; Schüssler et al., 2010). In one study, the observed differences with age were reported to be modest (Bauer, 1993). Reports of age-related decrease in renin, angiotensin, and aldosterone concentrations may contribute to the higher urine output at night.
Sex Differences in ANP, AVP, RAAS

Hvistendahl et al. found that young women had lower nocturnal levels of vasopressin compared to young men (Hvistendahl et al., 2007). In another study, plasma vasopressin concentration was always higher in men than in women (Asplund & Aberg, 1991). The effect of sex hormones on AVP and water homeostasis was investigated by Graugaard-Jensen and colleagues (Graugaard-Jensen, Hvistendahl, Frøkiaer, Bie, & Djurhuus, 2008). They reported that estrogen does not affect the daily rhythm of AVP, aldosterone, ANP, and subsequent urine output. Even without the effects of estrogen, a study by Stachenfeld et al. showing that women have higher renal sensitivity to AVP than men may explain the sex-related differences (Stachenfeld, Splenser, Calzone, Taylor, & Keefe, 2001). They also suggest that there is a change in the osmotic regulation during the menstrual cycle, possibly due to estrogen effects on AVP (Stachenfeld, Silva, Keefe, Kokoszka, & Nadel, 1999). Nocturia mainly affects older people, where the women are not having menstrual cycles, suggesting that there are other reasons that influence higher urine output. A greater sensitivity to vasopressin would promote water retention, which may contribute to possible sex differences in nocturia.

An analysis of a reference sample of 911 healthy subjects taken from the Framingham Heart Study showed that higher ANP levels were found in females (Dawber, Meadors, & Moore, 1951; Wang et al., 2002). The results of several studies of patients with cardiovascular problems demonstrated this same pattern (Alehagen, Svensson, & Dahlström, 2007; Hogenhuis et al., 2005; Luchner et al., 2002). However, in
one study of 216 healthy subjects 20 to 77 years of age, there was no significant
difference in the mean ANP value (Clerico et al., 2002).

Several studies have reported that plasma renin activity is lower in women than in
men (James et al., 1986; Kaplan et al., 1976; Sandberg & Ji, 2003; Schunkert et al., 1997;
Schüssler et al., 2010). The down-regulation of the RAAS system by estrogen has been
demonstrated more significantly through laboratory experiments, rather than in vivo
(Fischer, Baessler, & Schunkert, 2002; McGuire, Watson, Pérez-Barriocanal, Fitzpatrick,
& Docherty, 2007). One study found no significant sex-related differences in RAAS
between 85 year old subjects (Skøtt et al., 1987). They suggested that this could be due to
the lack of standardized methods to compare plasma hormone concentrations.

There are observed sex differences in ANP, AVP, and RAAS. Females tend to
have higher sensitivity to AVP and higher levels of plasma ANP. Males have higher
levels of PRA and plasma AVP. The sex-related differences of these hormones that affect
urine output suggest an unequal prevalence of nocturia.

Nocturia and Sleep

There are several factors of nocturia to consider. Diuretic medications and alcohol
may aggravate nocturia (“Nocturia,” 2013). Congestive heart failure and sleep apnea are
some of the many underlying medical problems that may exacerbate nocturia. After
controlling for wake times, and fluid and food intake using a Constant Routine protocol, a
significant difference in the circadian pattern of urine output was found between younger
and older subjects (Hares et al., 2007). The greater amount of the 24 hour urine output at
night in the older group suggested that age-related changes in the circadian rhythm of some of the hormones involved in urine production may lead to nocturia. One candidate is AVP, due to the disturbance in the diurnal variation of AVP, which was found to be a common cause of nocturia (Asplund & Aberg, 1991).

**Nocturia and Aging**

Many studies have shown a higher prevalence of nocturia with age. Several urological survey studies have examined self-reports of nocturia in different age groups. The vast majority of the oldest age group in the population will wake up at least once per night to void, while fewer than 20% have no reported symptoms of nocturia (Fonda, 2002). A study in Austria by Schatzl *et al.* found that the percentage of men and women that void two or more times per night consistently increases from 3% below 30 years to about 30% for those 60 years or older (Schatzl *et al.*, 2000). Chute *et al.* investigated the prevalence of urinary symptoms of prostatism in a Minnesota community and found that nocturia increases with age (Chute *et al.*, 1993). These findings agree with the results of population studies conducted in Denmark and Japan (Jensen, Jørgensen, Mogensen, & Bille-Brahe, 1986; Tsukamoto *et al.*, 1995). A study conducted in the Netherlands reported that nocturia is experienced by 62% of men 55-74 years of age, and by 80% of men older than 75 years, with similar findings in women (L. Van Dijk, Kooij, & Schellevis, 2002). Tikkinen *et al.* conducted a survey of 6,000 subjects in Finland from the ages of 18-79 and reported that the prevalence of at least 2 voids per night was less
than 10% for age 18-49, then more than doubles after age 60 (Tikkinen, Tammela, Huhtala, & Auvinen, 2006).

Individuals seem to be more affected by nocturia as they get older. Regular complaints of nocturia were reported by 4% of children aged 7–15, more than 55% for men and women aged 50–59, and 91% of men and 72% of women over 80 years (Mattsson, 1994; Middelkoop, Smilde-van den Doel, Neven, Kamphuisen, & Springer, 1996). Saito et al. found that in their study group elderly patients were more likely than the younger patients to have problems leading to nocturia (Saito, Kondo, Kato, & Yamada, 1993). While the 24 hour urine volumes were similar, the elderly had a lower daytime urine output and greater nocturnal urine output, with more frequent and smaller nocturnal voids. This might be explained by age-related changes in the urinary system, such as decreased functional bladder capacity (Asplund, 1999), increased post-residual urine volume (Madersbacher et al., 1998), and changes in the detrusor muscle (Elbadawi, Yalla, & Resnick, 1993).

**Nocturia and Gender**

Another factor to consider in nocturia is gender. There are physiological differences between men and women, some of which also affect the aging process. A survey of over 2,500 people in Austria showed that men and women are almost equally affected by nocturia (Schatzl et al., 2000). Jin and Moon found an insignificant difference in the prevalence of nocturia between men and women (Jin & Moon, 2008). A study by Middelkoop et al. reported that men had a greater prevalence of nocturia than women.
after the age of 50 (Middelkoop et al., 1996). Of the 6,000 participants surveyed, Tikkinen reported that the prevalence of nocturia in women is higher than men from the ages of 18 to 49, similar from the ages of 50-59, and higher in men from the ages of 60-79 (Tikkinen et al., 2006). The direct link of gender and nocturia is unclear, suggesting a greater need to elucidate the underlying mechanisms of nocturia.

**Role of Nocturia in Quality of Life**

Nocturia can reduce the hours of uninterrupted sleep at night, leading to more daytime sleepiness. Two surveys have found a high correlation between the self-reports of waking at night to void with symptoms of excessive daytime sleepiness (Daniel J Foley et al., 2007; Whitney et al., 1998). Nocturia can also lead to increased risk of injury from falling at night, depressive symptoms, and memory problems (Marinkovic, Gillen, & Stanton, 2004). There are even reports that survival rates are lower in individuals with nocturia (Varilla, Samala, Galindo, & Ciocon, 2011).

Nocturia has been reported as major cause of sleep disruption in sleep surveys. The 2003 National Sleep Foundation “Sleep in America” polled more than 1,500 American adults over the age of 55 (“Executive Summary of the 2003 Sleep in America poll,” 2003). The most common reported problem disturbing sleep of adults ages 55-84 is the need to get up to go to bathroom (Figure 3). Most reported experiencing this every night or almost every night. The report showed that the need to get up increases significantly with age. Nocturia was reported to be the second strongest predictor for self-reported poor sleep quality, and represented a 75% increased risk of self-reported
insomnia after correcting for significant co-morbidities (D. Bliwise et al., 2004). The Cardiovascular Health Study surveyed over 4,500 people over the age of 65 to describe the prevalence of daytime sleepiness in the elderly. About two-thirds of those surveyed (68% of women and 66% men) reported often waking up several times a night. The most prevalent reason of waking up was to go to the bathroom (89% men and 86% women) (Whitney et al., 1998). Improving the symptoms of nocturia have shown to improve the quality of life (Johnson et al., 2003).
Figure 3 – Symptoms Disturbing Sleep of Older Adults. Various causes of sleep disturbance of adults over the age of 55, with nocturia reported as the most common problem. Adapted from the 2003 Sleep Poll.
Chronic lack of sleep has many detrimental effects on the quality of life. Studies of people suffering from insomnia demonstrated how daytime performance declines, while medical illness and hospitalizations increase (Culpepper, 2006; Stanley, 2005). When nocturia is a comorbidity of insomnia, the impairments were larger (Hernández Fernández, Ristol Pont, Estivill, Batista Miranda, & López Aramburu, 2007; Hetta, 1999; Stanley, 2005). The prevalence of nocturia increases as comorbidities with conditions such as sleep disorders and obesity. A recent study of patients in the Boston area reported that nocturia is associated with a decreased quality of life and increased symptoms of depression (Kupelian et al., 2012). Asplund studied over 10,000 elderly and found that those with more than two nocturnal voids per night were more likely to have poor sleep, have cardiovascular disease and be diabetic (Asplund, 2006a). In an earlier study, Asplund found that the mortality rate of older people correlated with the number of nocturnal voiding episodes over a 4.5 year window of observation (Asplund, 1999). Reports of impaired quality of life was reported in 66.9% of women and 62.2% of men with nocturia (Schatzl et al., 2000).

Daytime impairment often affects occupational performance. Kobelt et al. have reported that those with nocturia had greater work impairment, which was significantly correlated with the severity of the condition (Kobelt, Borgström, & Mattiasson, 2003). Ohayon found that there were significantly more sick days for those waking up at least one night per week (Ohayon, 2008). Disturbance of sleep due to nocturia negatively affects work attendance and performance. Participants of one study reported more daytime sleepiness with more sleep disturbances (Whitney et al., 1998). Akerstedt et al.
found that the likelihood of involuntarily falling asleep at the workplace is connected to disturbed sleep at night (Akerstedt et al., 2002).

Many studies have shown that sleep disruption, such as with nocturia, have led to more accidents. Nocturia may cause fatigue in drivers, which is estimated to contribute to about 35% of accidents on the road after moderate sleep deprivation (Williamson & Feyer, 2000). Furthermore, older people with nocturia have a higher probability of falling, which might be due to going to the bathroom at night, or to daytime sleepiness (Nakagawa et al., 2008). A high percentage of elderly patients fall during their effort to void at night (Barker & Mitteness, 1988). One study showed a significant positive association between the number of voids per night and the prevalence of bone fracture (Asplund, 2006b). Another study found that the risk of hip fractures increases in men with nocturia independent of age (Schatzl et al., 2000).

**Treatment of Nocturia**

The current treatments available for nocturia depend on the etiology of the condition. Controlling fluid intake prior to bedtime is one of the many lifestyle changes that can reduce the symptoms of nocturia. Surgery is generally used when a significant causative factor of nocturia is the prostate or other anatomical pressures to void (Jin & Moon, 2008).

Generally, the easiest step to take is a change in lifestyle. Nocturia due to caffeine and alcohol can be avoided if these diuretics are restricted (Abrams et al., 2002). Restricting fluid intake before bedtime helps particularly for incontinence due to a strong
urge to void (Griffiths, McCracken, Harrison, & Gormley, 1992). However, a study by Asplund and Aberg have found that about half of those who woke up more than two times per night had already restricted their fluid intake (Asplund & Aberg, 1992). It seems, though, that fluid restriction is ineffective for cases of nocturnal polyuria and lower extremity edema (Jin & Moon, 2008). The edema in the leg may be responsible for the fluid retention that leads to nocturia (Laureanno & Ellsworth, 2010). Compression stockings are used to limit fluid retention in the lower extremities. Lifestyle changes might also include behavioral modification. Behavioral therapies primarily focus on alleviating bladder symptoms with bladder health promotion, and training to control bladder functions (Wyman, Burgio, & Newman, 2009). Evidence for pelvic floor muscle exercise and urge suppression is positive (Burgio, 2004; Burgio et al., 2002; Teunissen, de Jonge, van Weel, & Lagro-Janssen, 2004). Cho et al created an educational program as behavioral therapy that showed significant improvement of nocturia after the first behavioral modification program (Cho et al., 2012). Lifestyle interventions prevent mostly external influences on nocturia, which would not be effective for underlying causes like altered circadian rhythms. The most investigated and common treatment for nocturia, however, is pharmacotherapy.

The FDA has not approved any treatments directly for nocturia at this time. Still, there are a number of pharmacological interventions used to treat the symptoms of nocturia. Some of the more known pharmacological therapy for nocturia primarily target bladder capacity and urinary flow obstruction (T. Johnson, 2013). Bladder outlet obstruction can be alleviated by relaxing muscles with alpha blockers, which target the
alpha-1 receptors found in the prostate and base of bladder (“Alpha-blocker medications for prostatitis,” 2010). If the obstruction is in the urinary tract, 5-alpha-reductase activity is inhibited (“Alpha-blocker medications for prostatitis,” 2010). The type 2 form of 5-alpha-reductase is an enzyme that catalyzes the conversion of testosterone to dihydrotestosterone, which is primarily responsible for prostate development and a factor of benign prostatic hyperplasia (Steers, 2001). Johnson et al. found that alpha blockers for bladder outlet obstruction that less than 40% of the men having a 50% reduction in nocturia, and for urinary tract obstruction that the net benefits for nocturia to be small (T. M. Johnson 2nd et al., 2003, 2007). When nocturia is caused by detrusor overactivity, an anticholinergic medicine can be prescribed to relieve the muscle spasms (“Nocturia,” 2013). One study shows a significant improvement in sleep with a significant reduction in waking up to void (Hill, Khullar, Wyndaele, & Lheritier, 2006). The efficacy of anticholinergic therapy for detrusor overactivity has been shown in over 6,700 patients across over 50 studies (Hay-Smith, Herbison, Ellis, & Moore, 2002; Hill et al., 2006). However, Fitzgerald’s group found that anticholinergics were not effective in treating urge incontinence (Fitzgerald, Lemack, Wheeler, & Litman, 2008). Their conclusion points to the importance of determining the correct etiology of nocturia to properly treat the condition. Studies have shown that anticholinergics have insignificant benefits for nocturia, but may be more useful in combination with another drug (Ruggieri, Braverman, & Pontari, 2005).

Desmopressin is similar to vasopressin, with only two amino-acid substitutes, and is found to be effective and well-tolerated treatment for both men and women for
nocturnal polyuria (G Lose et al., 2004; Gunnar Lose, Lalos, Freeman, & van Kerrebroeck, 2003; Mattiasson, Abrams, Van Kerrebroeck, Walter, & Weiss, 2002). As an analogue of arginine vasopressin (AVP), desmopressin increases water reabsorption in the kidney, thus decreasing urine output. This synthetic hormone can help treat the diminished release of vasopressin in nocturnal polyuria, and protect against the increase in ANP with sleep (Ancoli-Israel, Bliwise, & Nørgaard, 2011). Asplund et al. have shown that reducing the frequency of nocturnal voids with desmopressin led to significantly more hours of undisturbed sleep (Figure 4) (Asplund, Sundberg, & Bengtsson, 1999). During a double-blind treatment phase of a study done by van Kerrebroeck et al., there was a significant increase in the duration of sleep time and reduction in nocturia frequency with desmopressin (Van Kerrebroeck et al., 2007). While the efficacy of desmopressin is strongly supported, the significance is highly specific to nocturnal polyuria.
Figure 4 – The Number of Nocturnal Voids After 2 Weeks of Desmopressin Treatment. Reproduced from (Ancoli-Israel et al., 2011).
It is important to know the etiology of nocturia to administer the correct treatments. Despite the convenience of behavioral and lifestyle treatments, these methods are not the most effective. Some pharmacological interventions are more effective because they directly treat the underlying cause. Yet treatments are not FDA approved for directly curing nocturia because some potential underlying causes of nocturia, such as disrupted sleep or altered circadian rhythmicity, have not been directly addressed as causes of nocturia. Another question to consider when treating nocturia is whether the patient is awoken at night by the urge to void or instead if the patient decides to void after waking up. Older people, who typically have lighter and more fragmented sleep, may awaken first and then decide to void. A few studies took this into consideration by targeting the brain to treat sleep fragmentation as a factor in nocturia. One study found that combining an alpha-blocker with a hypnotic medication was more successful in reducing reported nocturia frequency than just the alpha-blocker alone (Song & Ku, 2007). A study by Sugaya et al. found that walking exercise significantly decreased the number of nocturia episodes due to deepened sleep (with that deepened sleep likely raising the bladder arousal threshold) (Sugaya et al., 2007). While limited in evidence, these two studies recognized the need for further investigation of the factors contributing to nocturia. With a better understanding of the underlying causes of nocturia, clinicians can then more effectively treat nocturia.
Specific Aims

One of the most common causes of sleep disturbance is nocturia. Many studies show that the tendency to void during the night increases with age, and is affected by the sex of the individual. What remains uncertain is the etiology of these age- and sex-related differences. The prevalence of nocturia in literature has been inconsistently explained in the significance of day-night rhythms of diuretic and anti-diuretic hormones affecting urine output. What has been overlooked in much of the literature is the connection between nocturia and age- and sex-related changes in sleep and circadian rhythms.

Therefore, the aims of this study are to determine:

1. whether there is an association between urological complaints and sleep complaints in older men and women, and whether those complaints differ between older men and women. We will accomplish this by surveying patients visiting the Brigham and Women’s Hospital Department of Urology clinic. We will analyze the responses and investigate if there are sex- or sleep-related associations with urological complaints;

2. whether there is evidence for a circadian rhythm in any of the diuretic/anti-diuretic hormones that may contribute to day-night differences in urine output, and if any of those rhythms are altered with aging thus potentially contributing to nocturia. We will accomplish this by analyzing hormone data collected from young and older participants in an inpatient circadian rhythm study in Brigham and Women’s Hospital Division of Sleep Medicine. We will determine if a circadian rhythm is exhibited by these hormones, and if any age-related differences in the pattern of hormone release are present.
This study is designed to investigate the sleep disturbance symptoms, as well as circadian rhythms of hormone levels that might contribute to nocturia. These results could provide evidence for a new pathophysiological approach to relieve nocturia, contribute to the ongoing research in the urology and circadian rhythm fields, and increase awareness of a condition that can affect the quality of life of older adults.
METHODS

Questionnaire Study

Subjects in the questionnaire study were patients, 204 males (64.2±8.84 years) and 87 females (63.3±8.95 years), who were ≥50 years old with appointments at the Brigham and Women’s Hospital Division of Urology clinic. After arriving for their previously-scheduled appointment, the subjects were approached and asked to participate in the questionnaire study. Written consent was obtained from each participant. The protocols, which conform to the Declaration of Helsinki, were approved by the Human Research Committee at Partners HealthCare System.

Subjects were given four questionnaires: the Pittsburgh Sleep Quality Index (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) to measure subjective sleep quality from the past month, the Epworth Sleepiness Scale (Johns, 1991) to evaluate daytime sleepiness, the AUA Symptom Index (AUASI) (Barry et al., 1992) to evaluate urinary complaints, and a general questionnaire regarding health, naps, and medication. The questionnaires were scored according to published criteria. Higher scores on each of the questionnaires [PSQI, ESS, AUASI] indicate greater numbers of complaints.

The mean age of the men and women were compared using a t-test to determine whether their ages were significantly different. The link between urological complaints, daytime sleepiness, and sleep quality was investigated by analyzing questionnaire responses. The mean scores of the PSQI, ESS, and AUASI questionnaires were compared by conducting Levene’s Test for equality of variances and a t-test for equality of means.
to investigate any sex-related differences in reported quality of sleep, daytime sleepiness, and urological complaints.

Spearman’s correlation coefficient was used to explore the association between sleep–wake (daytime sleepiness and quality of sleep) and urological complaints. First, the PSQI and ESS questionnaire scores were compared with AUASI questionnaire scores to investigate how sleep or daytime sleepiness impacts urological symptoms. Then, the PSQI questionnaire scores were compared with ESS questionnaire scores to identify any associations between sleep quality and daytime sleepiness.

The relationship between test scores was quantified with a multivariate linear regression analysis. The extent of how well one questionnaire can predict the results from the two others was tested. Statistical tests were run using SPSS® software.

**Hormone Study**

Subjects in the hormone study were ten young (9M, age: 23.1±2.81) healthy individuals who were ≥18 years old, and nine older (6M, age: 58.9±4.65) healthy individuals who were 55 – 80 years old, who were screened to participate in a research study at Brigham and Women’s Hospital Division of Sleep Medicine. In both age groups, those with sleep, psychiatric, or active medical disorders were excluded. Subjects were recruited by ads in flyers, newspapers, and on the web. Written informed consent was obtained from each participant. The protocols, which conform to the Declaration of Helsinki, were approved by the Human Research Committee at Partners HealthCare System.
Subjects had three baseline days to adjust to the laboratory environment, and then underwent a constant routine (CR) circadian phase and amplitude assessment procedure. The baseline days consisted of 16 hours of wakefulness and 8 hours of time in bed in the dark, scheduled at each person’s habitual times. The CR began at wake time after the third night, and consisted of continuous wakefulness, in constant dim light (3 lux), in a controlled and constant posture (head of bed elevated to ~45° with knees raised), low activity level, constant room temperature (~75° Fahrenheit), a time-free environment, food and liquid in equicaloric hourly aliquots throughout day and night, and collection of blood, saliva and urine samples at regular intervals. A trained staff member remained in the room with the participant throughout the CR to ensure they followed the protocol instructions and to assist them in remaining awake. In the young group, the CR lasted for 40 hours, while in the older group it lasted 27 hours.

The meals for baseline days were *ad lib* with 16 oz. water provided with each meal. The older subjects were allotted 150 mEq Na⁺/100 mEq K⁺ (± 20%) controlled nutrient, isocaloric diet, and 2500 mL fluids for each meal on their third baseline day. During the constant routine, the participants received hourly meals that provided 150 mEq Na⁺/100 mEq K⁺ (± 20%) controlled nutrient, isocaloric diet, and 2500 mL fluids each 24 hours. The participants were required to eat all the food and drink all the fluids during the CR.

Blood samples were collected every four hours from the young and older subjects throughout the CR. The blood samples were immediately processed and frozen, and later assayed for aldosterone, AVP, ANP, and PRA.
Plasma aldosterone was measured by a radioimmunometric assay (RIA) with the Coat-A-Count procedure through Siemens Medical Solutions Diagnostics. The sensitivity of this method is 11 pg/mL. The intra-assay precision is 3.3% and the inter-assay precision is 8.4%.

Plasma ANP was measured by an RIA kit manufactured by the American Laboratory Products Company. The sensitivity of this method is 3.5 pg/mL. The intra-assay precision is 8.6% and the inter-assay precision is 11.6%.

Plasma AVP was measured by double anti-body RIA with the Buhlmann Vasopressin RIA “Ultra Sensitive” and Direct RIA kits manufactured by the American Laboratory Products Company. For Direct RIA, the sensitivity is 0.75 pg/mL, the intra-assay precision is 6.0%, and the inter-assay precision is 9.9%. For RIA “Ultra Sensitive”, the sensitivity is 0.39 pg/mL, the intra-assay precision is 7.6%, and the inter-assay precision is 10%.

Plasma renin activity was measured by an RIA kit manufactured by Diasorin, Inc. The intra-assay variation is 4.6-10%, and the inter-assay variation is 5.6-7.6%. The sensitivity is not reported.

We averaged the plasma hormone data across participants in each age group in 4-hour bins and plotted them to visually inspect whether there was any apparent rhythmicity. To confirm whether a significant circadian rhythm was present, we performed cosinor analysis using SAS® software.
RESULTS

Questionnaire Study

The groups of men and women were not significantly different in age (See Table 1 and Figure 5).

Table 1 –Age and Questionnaire Scores of Females and Males. N = number of subjects, SD = Standard Deviation, PSQI = Pittsburgh Sleep Quality Index, ESS = Epsworth Sleepiness Scale, AUASI = American Urological Association Sleep Index.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Age</th>
<th>SD</th>
<th>PSQI</th>
<th>SD</th>
<th>ESS</th>
<th>SD</th>
<th>AUASI</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>87</td>
<td>63.27</td>
<td>8.95</td>
<td>7.21</td>
<td>4.84</td>
<td>5.91</td>
<td>4.75</td>
<td>14.83</td>
<td>10.0</td>
</tr>
<tr>
<td>Male</td>
<td>204</td>
<td>64.17</td>
<td>8.84</td>
<td>5.26</td>
<td>3.43</td>
<td>5.94</td>
<td>4.31</td>
<td>11.73</td>
<td>7.97</td>
</tr>
</tbody>
</table>

Figure 5 – Mean Age of Males versus Females. Age of males on the left and of females on the right.
The mean PSQI score for the men was 5.26±3.43 and for women was 7.21±4.84 (See Table 1 and Figure 6). An equality of variance test showed that the variability between mean PSQI scores of men and women were significantly different (p < 0.01). A two-tailed t-test with unequal sample variances showed that the mean PSQI scores were significantly higher in the women than in the men (p < 0.01), indicating greater sleep complaints in the women. See Table 2.

Figure 6 – Mean PSQI Scores of Males Versus Females. PSQI scores of males on the left and of females on the right. Females have significantly greater variability and a significantly higher mean score than males, indicating greater sleep complaints.
The mean ESS score for males was 5.94±4.31 and for females was 5.91±4.75 (See Table 1 and Figure 7). An equality of variance test showed that the variability between mean ESS scores of men and women were not significantly different (p = 0.258). A two-tailed t-test with equal sample variance showed that the mean ESS scores between men and women were not significantly different (p = 0.969). See Table 2.

![Figure 7 – Mean ESS Scores of Males Versus Females. ESS score of males on the left and of females on the right. Mean scores and variability were not significantly different between the two groups.](image-url)
The mean AUASI score for males was 11.7±7.97 and for females was 14.83±10.0 (See Table 1 and Figure 8). An equality of variance test showed that the variability between mean AUASI scores of men and women were significantly different (p < 0.01). A two-tailed t-test with unequal sample variance showed that the mean AUASI scores were significantly greater in the women than in the men (p = 0.012), indicating that the women had more urological complaints. See Table 2.

![Figure 8](image_url)  

**Figure 8 – Mean AUASI Scores of Male versus Female.** AUASI score of males on the left and of females on the right. Females had significantly greater variability and a significantly higher mean score than males, indicating greater urological complaints.
Table 2 – Test for Equality of Variances and Equality of Means between Genders of PSQI, ESS, and AUASI Scores. The variability between mean PSQI scores of men and women were significantly different. The variability between mean ESS scores of men and women were not significantly different. The variability between mean AUASI scores of men and women were significantly different.

<table>
<thead>
<tr>
<th></th>
<th>F</th>
<th>Sig.</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI</td>
<td>15.84</td>
<td>0.000</td>
<td>-3.402</td>
<td>124.47</td>
</tr>
<tr>
<td>ESS</td>
<td>1.282</td>
<td>0.258</td>
<td>0.039</td>
<td>289</td>
</tr>
<tr>
<td>AUASI</td>
<td>8.271</td>
<td>0.004</td>
<td>-2.56</td>
<td>134.755</td>
</tr>
</tbody>
</table>

A Spearman’s rank-order correlation coefficient was computed to further assess the relationship between sleep quality, daytime sleepiness, and urological complaints among the women (Table 3). There was only a weak, positive correlation between PSQI and AUASI questionnaire scores (see Figure 9), suggesting that poorer sleep quality was associated with more urological complaints in the women. There was no significant correlation found between ESS and AUASI questionnaire scores, suggesting that daytime sleepiness was not associated with urological complaints. There was no significant correlation found between PSQI and ESS questionnaire scores either, suggesting that sleep quality was not associated with daytime sleepiness.
Table 3 – Spearman’s Correlation Coefficient between PSQI, ESS, and AUASI in Women. There was no significant correlation between sleep quality and daytime sleepiness, and daytime sleepiness and urological complaints. There was a significant correlation between sleep quality and urological complaints.

<table>
<thead>
<tr>
<th>Spearman's rho</th>
<th>Correlation Coefficient</th>
<th>Sig. (2-tailed)</th>
<th>N</th>
</tr>
</thead>
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<tr>
<td>PSQI</td>
<td>Correlation Coefficient</td>
<td>1</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>0.949</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>ESS</td>
<td>Correlation Coefficient</td>
<td>0.007</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.949</td>
<td>.</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>86</td>
<td>86</td>
</tr>
<tr>
<td>AUASI</td>
<td>Correlation Coefficient</td>
<td>.325*</td>
<td>0.028</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.002</td>
<td>0.797</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>86</td>
<td>86</td>
</tr>
</tbody>
</table>

* = p < .01
Figure 9 – Female AUASI Scores Plotted Against PSQI Scores. There is a positive correlation between PSQI and AUASI scores in females.

Multivariate linear regression modeling found that when the PSQI score increased by 1 in women, the AUASI score increased by a mean value of 0.154 \( t(84) = 3.0628, p = 0.003 \). When the AUASI score increased by 1 in women, the PSQI score increased by mean value of 0.660 \( t(84) = 3.0628, p = 0.003 \). See Table 5 and Figure 9. In women, urological complaints are a stronger predictor of sleep quality than vice versa.
Table 4 – Descriptive Statistics of Multivariate Linear Regression Modeling in Women. The overall fit model predicting PSQI scores significantly shows that ESS and AUASI scores can account for 10.2% of the variance in PSQI scores. The overall fit model predicting AUASI scores significantly showed that PSQI and ESS scores can account for 10.2% of the variance in AUASI scores. The overall fit model predicting ESS scores did not significantly show that PSQI and AUASI scores can account for the .1% of the variance in ESS scores.

<table>
<thead>
<tr>
<th>Predictor Variables</th>
<th>Unstandardized Coefficients (B)</th>
<th>Overall Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSQI</td>
<td>ESS</td>
</tr>
<tr>
<td>PSQI</td>
<td>0.017</td>
<td>0.154*</td>
</tr>
<tr>
<td>ESS</td>
<td>0.019</td>
<td>0.011</td>
</tr>
<tr>
<td>AUASI</td>
<td>0.660*</td>
<td>0.045</td>
</tr>
</tbody>
</table>

* = p < .05

A Spearman’s rank-order correlation coefficient was computed to further assess the relationship between PSQI, ESS, and AUASI scores among the men (Table 5). There was a positive correlation between PSQI and AUASI questionnaire scores, ESS and AUASI questionnaire scores, PSQI and ESS questionnaire scores in men. Decreased quality of sleep reported through PSQI was correlated with increased daytime sleepiness in males. Increased daytime sleepiness was correlated with increased urological complaints in males. Decreased quality of sleep was correlated with increased daytime sleepiness in males.
There was a significant correlation between sleep quality and daytime sleepiness, sleep quality and urological complaints, and daytime sleepiness and urological complaints.

### Table 5 – Spearman’s Correlation Coefficient between PSQI, ESS, and AUASI in Men.

There was a significant correlation between sleep quality and daytime sleepiness, sleep quality and urological complaints, and daytime sleepiness and urological complaints.

<table>
<thead>
<tr>
<th></th>
<th>PSQI</th>
<th>ESS</th>
<th>AUASI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Correlation Coefficient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>.</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>203</td>
<td>203</td>
</tr>
<tr>
<td><strong>Correlation Coefficient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.266*</td>
<td>1.00</td>
<td>0.233*</td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>203</td>
<td>203</td>
</tr>
<tr>
<td><strong>Correlation Coefficient</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sig. (2-tailed)</td>
<td>0.339*</td>
<td>0.233*</td>
<td>1.00</td>
</tr>
<tr>
<td>N</td>
<td>203</td>
<td>203</td>
<td>203</td>
</tr>
</tbody>
</table>

* = p < .01

Multivariate linear regression modeling found that the PSQI score increased by 1 in men, the ESS score increased by a mean value of 0.293 [t(201) = 3.248, p = 0.001] and the AUASI score increased by a mean value of 0.723 [t(201) = 4.542, p = 0.000]. For each ESS score increased by 1 in men, the PSQI score will increase by a mean value of 0.171 [t(201) = 3.248, p = .001]. For each AUASI score increased by 1 in men, the PSQI score will increase by a mean value of 0.129 [t(201) = 4.542, p = .000]. See Table 6 and Figure 10, 11. In men, sleep quality is a stronger predictor of daytime sleepiness and urological complaints than vice versa.
Figure 10 – Male PSQI Scores Plotted Against ESS Scores.

Figure 11 – Male PSQI Scores Plotted Against AUASI Scores.
Table 6 – Descriptive Statistics of Multivariate Linear Regression Modeling in Men.
The overall fit model predicting PSQI scores significantly shows that ESS and AUASI scores can account for 16.2% of the variance in PSQI scores in men. The overall fit model predicting ESS scores significantly shows that PSQI and AUASI scores can account for 8.9% of the variance in ESS scores in men. The overall fit model predicting AUASI scores significantly shows that PSQI and ESS scores can account for 13% of the variance in AUASI scores in men.

<table>
<thead>
<tr>
<th>Male</th>
<th>Unstandardized Coefficients (B) of Predictor Variables</th>
<th>Overall Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PSQI</td>
<td>ESS</td>
</tr>
<tr>
<td>PSQI</td>
<td>0.171*</td>
<td>0.129*</td>
</tr>
<tr>
<td>ESS</td>
<td>0.293*</td>
<td>0.121</td>
</tr>
<tr>
<td>AUASI</td>
<td>0.723*</td>
<td>0.116</td>
</tr>
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</table>

* = p < .05
**Hormone Study**

The plasma hormone data were averaged into 4 hour bins and plotted. We detected an apparent rhythmicity in the young subjects (Figure 12). There was a decline in hormone levels from wake time (0h) to 16h awake, corresponding to the usual waking day. Then the levels rose throughout the nighttime and began to decline again at approximately 24h awake, corresponding to usual wake time. The 40h point was omitted from the dataset because some of the samples were collected after bedtime, and not during the CR.

![Graph showing plasma aldosterone levels in young subjects](image)

**Figure 12 – Mean Plasma Aldosterone Levels in Young Subjects.** The plasma aldosterone concentrations in young subjects were recorded during their 40 hour constant routine.

We did not detect any apparent rhythmicity in the older subjects (Figure 13). There was a decline from wake time (0h) to 12h awake, corresponding to the usual waking day. Then the levels rose to 16h awake, which still corresponds to the usual
waking day. The levels fell until 20h awake, corresponding to the usual nighttime. The levels rose back up until 24h awake, which begins the usual wake time.

**Figure 13 – Mean Plasma Aldosterone Levels in Older Subjects.** The plasma aldosterone concentrations were recorded in older subjects during their 27 hour constant routine.

Cosinor analysis was performed on the aldosterone data to check the significance of any present circadian rhythm. The rhythm of young subjects fit to the cosine model, and thus demonstrated a significant circadian rhythm ($F_{2,7} = 16.204, p < 0.01$). The rhythm of older subjects did not significantly fit to the cosine model, and thus did not demonstrate a significant circadian rhythm ($F_{2,7} = 2.10, p = 0.238$).
DISCUSSION

Questionnaire Study

The mean age between men and women was not significantly different. This suggests that in our study, we did not have to consider the confounding influence of age in our analysis.

The PSQI quantifies subjective reports of sleep quality. Studies show that men have a higher likelihood of arousal at night and women having higher baseline SWA levels. This suggests that men would have lower quality of sleep, yet our data shows women scoring higher on the PSQIs, indicating greater sleep complaints. This agrees with studies that show that women tend to report greater sleep disturbances than age-matched men (M V Vitiello, 2000; Michael V Vitiello, Larsen, & Moe, 2004), and even when their objective sleep appears to be of better quality. Future studies interested in these results should refer to previous studies that have already compared the subjective reports with objective sleep measures, such as SWA and REM.

The ESS characterizes daytime sleepiness. We found that daytime sleepiness reports were not significantly different between men and women. Without specifying the conditions for each question, it is difficult to ascertain whether the events coincide with the strong sleep drive in the afternoon. Furthermore, daytime sleepiness can be caused by poor sleep from the previous night, may change the sleep quality of the night of, or may be influenced by physiological disturbances.

Nocturia was commonly characterized as a condition only found in men and related to BPH. Now it is well accepted that nocturia is found in both men and women.
Studies have reported that older women have higher prevalence of nocturia than men in the same age group. Based on the AUASI scores, we found that women had significantly more urological complaints than men in our study. Further analysis of the questionnaire results should be conducted to understand whether the women in our study had more chronic medical conditions, were taking medications, were pregnant, or had other reasons for having greater urological complaints than the men.

PSQI score was a stronger predictor of AUASI score than vice versa in both men (.723 > .129) and women (.66 > .154) – a correlation stronger in men than in women (.723 > .66). This may mean that men have lighter sleep, and thus are more vulnerable to nocturnal voiding problems. In general, older men spend less time in the deepest stages of sleep than do older women, which may have contributed to the greater sleep disturbances reported here (Redline et al., 2004; Sheldon, Ferber, & Kryger, 2005). This would agree with our finding of how AUASI scores are stronger predictors of PSQI scores in women than in men (.154 > .129). Prior studies suggest that women have higher sensitivity to AVP and have higher levels of plasma ANP, which would contribute to greater urine output. Stronger hormonal influences to void may explain why urological complaints are stronger predictors of sleep quality in women than in men. Despite finding a correlation between sleep quality and urological complaints, we could not determine whether being awakened at night is due to poor sleep quality or the urge to void. Future studies should be conducted to determine if voiding follows awakening, or vice versa.

We found that male PSQI scores predict ESS scores better than vice versa (.293 > .171). Poor sleep quality influencing daytime sleepiness agrees with the scientific
literature. Because we found this correlation only in men, this might suggest that men are more prone to the consequences of drowsiness during the day. It is also important to note the direction of prediction. Daytime drowsiness did not predict poorer sleep quality, which supports the literature of sleep fragmentation causing drowsiness the next day. A well-reported cause of interrupted sleep is urinary dysfunction. Our finding of daytime sleepiness prediction only in men might indicate that men are more affected by their urological complaints, and thus have a greater tendency to report it.

In our study, we did not find a significant correlation of ESS scores with PSQI or AUASI scores in women. This might be due to the smaller sample size (87F versus 204 M). By increasing the number of female respondents in the future, one might find daytime sleepiness associated with sleep quality or urological complaints, and may be more closely investigated.

**Hormone Study**

We found a circadian rhythm of aldosterone that is independent of sleep in young adults. While this agrees with the general literature, it is important to note the present results disagree with the results from one particular study. Brandenberger’s group reported that the diurnal rhythm in aldosterone secretion is dependent on sleep, rather than an endogenous circadian rhythm (Charloux et al., 2001; Charloux, Gronfier, Lonsdorfer-Wolf, Piquard, & Brandenberger, 1999). Their study design differed from ours, in that subjects were either sleep-deprived or had their sleep shifted to daytime hours. Their study may not have adequately controlled for all the influences on circadian
rhythms. In contrast, our study subjects followed a Constant Routine for at least 24 hours, with controlled fluid and food intake spread throughout day and night, constant posture, lighting, room temperature, and wakefulness. A Constant Routine protocol minimizes various exogenous effects to more accurately observe the output of the internal clock (Duffy & Dijk, 2002; Minors & Waterhouse, 1984). While we did observe a circadian rhythm of aldosterone secretion in young subjects, we cannot determine why there was an absence of a circadian rhythm in older subjects. It may be due to the shorter duration of sample collection in the older subjects, due to the different sex distribution of the two age groups, or possibly due to an age-related attenuation of nocturnal aldosterone secretion (Asplund & Aberg, 1991; Ouslander et al., 1998). If the latter is the case, then the observed circadian rhythm of aldosterone in the younger subjects and absence in the older subjects may explain why there is a greater prevalence of nocturia with age.

Although there are reported circadian patterns of ANP and PRA secretion, we were unable to detect this in our study (Cugini et al., 1992a; Maggioni, Lucini, Antinozzi, & Pagani, 2001; Mulrow & Ganong, 1961; Portaluppi et al., 1990; Rittig et al., 1991). The lack of circadian rhythm of ANP in older subjects of our study agrees with the reports of ANP circadian rhythm lost in the elderly (Cugini et al., 1992). The older subjects in Cugini’s group still showed rhythms in aldosterone and renin secretion, suggesting that the inhibitory action might be lost. The inhibitory effect that ANP has on the renin-angiotensin-aldosterone system may contribute to the higher prevalence of nocturia with age. Both studies used constant routines to control for exogenous influences but there were still differences in the results. However, we also did not detect a rhythm in ANP in
the young subjects in our study, suggesting either a problem with the ANP sample collection or assay procedures, or a lack of rhythmicity in ANP under well-controlled constant conditions.

ANP is released in response to high blood pressure in order to reduce the hemodynamic pressure of water and sodium on the system. A strictly controlled diet is necessary to monitor the effects of any change in blood pressure caused by food and fluid intake. One study showed that subjects with no sodium restriction had clearance rates of ANP that were closely related to their sodium intake (Iervasi et al., 1993). Similarly, plasma ANP levels were higher in high salt intake groups relative to low salt intake groups (Houben et al., 1998). Sodium levels affect ANP activity, and ANP is an inhibitor of aldosterone and renin secretion. Therefore, the diet also affects the plasma aldosterone and renin concentration. It was observed that ANP is a stronger inhibitor of aldosterone (Dessi-Fulgheri et al., 1999). Nevertheless, the inhibitory actions of ANP may suggest that there is an amplified physiological effect of diuresis, and in turn, nocturia. The controlled diet and nutrition for our subjects may need to be adjusted in order to prevent masking any circadian rhythm for ANP. A detailed investigation of the hemodynamic changes would ANP would also help future studies. If we found evidence of higher ANP levels at night in older subjects, this would help explain the greater prevalence of nocturia in older subjects.

The absence of a circadian rhythm of PRA in our subjects may be due to the well documented age-related decline in the amount of slow-wave sleep per night (Carskadon & Dement, 2011). Less slow-wave sleep would shorten the amount of NREM sleep. Few
studies have shown that plasma renin activity follows an ultradian rhythm where the levels rise during NREM sleep, and fall during REM sleep (Brandenberger et al., 1994; Brandenberger, Follenius, Simon, Ehrhart, & Libert, 1988; Lightman et al., 1981). A recent study has shown the same ultradian rhythm of plasma renin activity (Schüssler et al., 2010). However, these studies did not utilize the constant routine with adequate adjustment days to accurately detect a circadian rhythm.

During a Constant Routine, subjects are deprived of sleep. Sleep deprivation in healthy children resulted in significantly more urine output, lower levels of plasma AVP, renin, angiotensin II, and no change in aldosterone, relative to normal sleep (Mahler et al., 2012). These changes lead to less sodium and water reabsorption in the kidney, and thus more urine output and nocturia. Adult men also appeared to have excess nocturnal urine output during sleep deprivation (Kamperis, Hagstroem, Radvanska, Rittig, & Djurhuus, 2010). Acute sleep deprivation has significant effects on urine output in both the young and old. This should be further investigated in order to better understand data from a routine that helps unmask external influences on circadian rhythms.

Overall, in the questionnaire study, we found that poorer sleep quality was associated with more urological complaints in both women and men. In men, daytime sleepiness was also correlated with urological complaints, and decreased quality of sleep was correlated with increased daytime sleepiness. In the hormone study, we found evidence for a sleep-independent increase in aldosterone levels at night, suggestive of an underlying rhythm in aldosterone secretion.
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Education

Boston University, Boston, MA | 2011-Present
Master of Arts in Medical Sciences

University of Illinois, Urbana, IL | 2007-2011
Bachelor of Arts in International Studies: Global Health
Minor in Chemistry

Cegrí Language School, Granada, Spain | Spring 2010
Spanish language & culture

Sendagaya Language School, Tokyo, Japan | June 2007
Japanese language

Employment History

Clinical Investigation Technician, Division of Sleep Medicine | 2012 – Present
Brigham and Women’s Hospital, Boston, MA
• Carry out major experimental protocol events, including bedtimes, wake times, light exposure sessions and constant routines
• Monitor data collection equipment, such as vital signs, sleep/wake cycles, and EEG
• Administer written and computerized tests of performance, memory, and alertness

Biochemistry Tutor, Division of Graduate Medical Sciences | 2012
Boston University School of Medicine, Boston, MA
• Tutor current students in graduate level biochemistry
• Position only offered to students who received an ‘A’ in the course

Consultant, Campus Information Technology and Education Services (CITES) | 2009-2011
University of Illinois, Urbana, IL
• Communicate with people of varying technical expertise
• Provide walkup, phone, online chat, and email consulting for CITES services and other computing needs
• Exhibit written and oral communication skills through customer service
• Entrusted with sensitive information to be treated in a conscientious manner

Medically Relevant Experience

Patient Advocate, Development Analyst Intern | 2012 – Present
Health Leads Boston at Boston Medical Center, Boston, MA
• Connect low-income families of the Pediatrics Department to resources that enable them to avert health crises and to access opportunities for income and education
• Develop an understanding of the health care system and preventative services
• Work in conjunction with social workers, nurses, physicians, legal aid workers and other clinical staff to ensure that patients can get and stay healthy
• Research and present individual and foundation prospects for Health Leads Boston

Observation | 2010 – 2011
Summer 2010 – Dr. Kwang-Sun Lee – NICU
University of Chicago. Chicago, IL
Summer 2011 – Dr. Adhir Shroff – CCU
University of Illinois. Chicago, IL
  • Better understand the medical team cohesion and hospital dynamics by following rounds
  • Visit and observe procedures in echo lab and cardiac catheterization lab

Spring 2011 – Emergency Department and Ambulance
Provena Covenant Medical Center, ProAmbulance. Champaign, IL
  • Practiced taking vitals and reports in a clinical setting
  • Discerned delegation of responsibilities in an emergency setting

Researcher | 2009 – 2011
Research partner: Regina Wang; Supervisor: Dr. Weimo Zhu, Kinesiology
University of Illinois. Urbana, IL
  • Obtain a better understanding of the influential factors that affect cancer patients by using complementary and alternative medicine (CAM) through a self-directed process
  • Investigate the prevalence of CAM among cancer patients of China and United States
  • Harvest data from Shanghai Cancer Rehabilitation School in Shanghai, China
  • Collect data from past studies in China and US and research for future publication
  • Presentation at a Global Studies poster session

Volunteer | 2009 – 2011
Inpatient & Emergency Department at Carle Foundation Hospital. Urbana, IL
  • Maintain patient confidentiality as per HIPAA
  • Provide extra assistance to staff by ensuring patient comfort and organizing stock rooms
  • Observe physician-patient interactions

Summer 2010
Institute of Tuberculosis Research, College of Pharmacy at University of Illinois. Chicago, IL
  • Observed laboratory techniques used in the discovery and development of effective, low-cost therapeutics for the treatment of tuberculosis

Spring 2010
Supervisor: Dr. José Manuel Jiménez López, Molecular Biology and Biochemistry
University of Granada. Granada, Spain
  • Observed laboratory techniques used to investigate cellular cholesterol transport and alkyl phospholipid analogues as antitumor agents
• Attended a seminar on new technologies in proteomics
• Translated scientific language from Spanish into English

Summer 2009
Director: Prabir Das
Bulbulir Basa Orphanage. Kolkata, India
• Tutored English, mathematics, and social science to 13 orphans from 6-11 years old
• Treated minor injuries including abrasions and infections
• Assisted in daily activities such as organizing events and chores

Certifications & Training
Emergency Medical Technician - Basic | Fall 2011
Illinois Department of Public Health, National Registry of Emergency Medical Technicians

American Heart Association: Basic Life Support Healthcare Provider | December 2010
Parkland Community College. Champaign, IL

Blood-Borne Pathogens, Hazardous Materials, & BSC Training | Summer 2010
University of Illinois, Chicago, IL

Institutional Reviews Board certification | Spring 2009
University of Illinois, Urbana-Champaign, IL

Honors & Awards
Seoul National University Alumni Association Scholarship | Fall 2011
Senior 100 Honorary | Spring 2011
Dean’s List | Fall 2010-Spring 2011
James Scholar Honors program | 2007-2008

Clubs & Organizations
President, Vice-President | 2008-2011
Korean American Student Association
• Restructured the organization to increase Korean-awareness on campus through numerous cultural activities
• Direct weekly board meetings and ensure functionality of organization as a whole
• Promote Asian-awareness through joint efforts with other organizations in the Asian Pacific American Coalition

Vice-President, Judicial Chair, Pledge Educator | 2008-2011
Chi Sigma Tau Fraternity, Inc.
• Contacted and worked with various organizations to encourage mutual support
• Delegated responsibilities across 12 chairs and committees
• Reinforced punctuality and
• Directed weekly executive board meetings
• Coordinated local and national membership recruitment
General Member | 2010-2011
Order of Omega – Greek Leadership Honors Society
- Plan events for the community to promote leadership
- Hosted a dodge ball tournament to raise money for abused children
- Required to be academically ranked above the all-Greek average GPA