Association Between Sleep and Morning Testosterone Levels In Older Men

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Study Objectives: The circulating testosterone levels of healthy men decline with advancing age. This process is characterized by considerable inter-individual variability, the causes of which are of significant biological and clinical interest but remain poorly understood. Since sleep quantity and quality decrease with age, and experimentally-induced sleep loss in young adults results in hormonal changes similar to those that occur spontaneously in the course of aging, this study examined whether some of the variability in circulating testosterone levels of older men can be related to objective differences in their sleep.

Design: Observational study.

Setting: General community and university clinical research center.

Participants: Twelve healthy men ages 64 to 74 years.

Interventions: Three morning blood samples were pooled for the measurement of total and free testosterone. In addition to overnight laboratory polysomnography, wrist activity monitoring for 6-9 days was used to determine the amount of nighttime sleep of the participants in everyday life settings.

Measurements and Results: The main outcome measures were total sleep time and morning testosterone levels. Sleep time in the laboratory was correlated with the usual amount of nighttime sleep at home (Pearson's r = 0.842; P = 0.001). Bivariate correlation and multiple linear regression analyses revealed that the amount of nighttime sleep measured by polysomnography was an independent predictor of the morning total (Beta 0.792, P = 0.017) and free (Beta 0.741, P = 0.029) testosterone levels of the subjects.

Conclusions: Objectively measured differences in the amount of nighttime sleep are associated with a significant part of the variability in the morning testosterone levels of healthy older men.

Key words: aging, androgens, polysomnography

Citation: Penev P. Association between sleep and morning testosterone levels in older men. *SLEEP* 2007;30(4):427-432.

INTRODUCTION

THE CIRCULATING TESTOSTERONE LEVELS OF HEALTHY MEN DECREASE ON AVERAGE BY 1-2% A YEAR STARTING IN THE THIRD TO FOURTH DECADE OF life.[1-3] However, some octogenarians continue to maintain androgen concentrations that are usually seen in young adults. Since the age-related decline in circulating androgen levels has been associated with metabolic disorders, decreased bone density, increased frailty and higher risk of falls with fractures, the factors responsible for the large variability of testosterone levels in older men are of considerable biological and clinical interest, but remain poorly understood.[4-6]

Chronic sleep changes are commonly seen in older adults. In the course of aging sleep architecture becomes increasingly fragmented by frequent arousals and awakenings, which leads to an overall reduction in sleep consolidation and in the total amount of sleep.[7] Axelsson et al[8] recently demonstrated that a period of either nighttime or daytime sleep in healthy young men is accompanied by an exponential rise in their testosterone concentrations, leading the authors to speculate that sleep plays an important role in determining the concentration of androgens in the circulation. Studies of total sleep deprivation in young male volunteers have reported a rapid decline in the circulating androgen levels of the participants.[9,10] Additional data indicate that the experimental fragmentation of sleep in young adults can also disrupt the usual rise of blood testosterone levels during the night.[11] Consistent with these observations, nighttime testosterone secretion is decreased in middle-aged men,[12] a demographic group already affected by the onset of age-related decrements in sleep quantity and quality.[13] Given the similarity between the changes in circulating androgen levels that occur spontaneously in the course of aging and those found in young adults under conditions of experimental sleep disruption or loss, this study tested the hypothesis that the large inter-individual variability in morning testosterone levels of healthy older men is related in part to objective differences in their sleep.

METHODS

Twelve nonobese self-sufficient male nonsmokers between the ages of 64 and 74 years completed the study. Study participants lived independently in the community and were recruited through local newspaper advertisements and by word of mouth. A total of 20 research volunteers were evaluated, and 8 of them were excluded during the screening phase of the study due to the presence of confounding medical problems. The remaining 12 subjects were healthy, based on their medical history, physical examination, Mini-Mental State Evaluation (MMSE)[14] and 15-item Geriatric Depression Scale (GDS)[15] scores, electrocardiogram, and results from laboratory testing including complete blood counts, fasting lipid, thyroid and comprehensive metabolic panels, prostate specific antigen (PSA) level, and urinalysis. Study participants did not take prescription medications except for one subject with a history of borderline hypertension, who was treated with 5 mg of Enalapril daily, and one subject with a history of primary hypothyroidism that was well-controlled with 0.112 mg of Levothyroxine daily. None of the participants reported taking

Disclosure Statement

Dr. Penev has indicated no financial conflicts of interest.

Submitted for publication May 2006

Accepted for publication November 2006

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any over-the-counter medications or health store supplements that could affect their sleep or gonadal function. Subjects with irregular life habits, self-reported sleep problems (Pittsburgh Sleep Quality Index,[16] PSQI score > 10), shift or night work schedules, habitual daytime naps, recent (< 4 weeks) travel across time zones, excessive alcohol (> 10 drinks/week) or caffeine (> 300 mg/day) use, above average exercise levels (> 3 hours/week), and any active medical, endocrine, metabolic, neurological, or psychiatric disorder were excluded from participating in the study. The research protocol was approved by the University of Chicago Institutional Review Board. All volunteers gave written informed consent and were paid for completing the study.

During an initial screening visit, 3 fasting blood samples were collected from each study participant at 15-20 minute intervals between 08:30 and 09:30. Screening was scheduled on a random weekday (Monday through Friday) according to individual preference. All screening visits followed a night of usual sleep quantity and quality at home according to the self-report of the subjects. Outpatient blood sample collection was done in the morning when circulating androgen levels are around their peak: such morning time sampling for androgen measurements is recommended in the clinical setting and routinely used in epidemiological studies.[3] Plasma aliquots from each of the 3 samples collected from the same individual were pooled together to obtain a single specimen for the measurement of his total and free testosterone concentrations in the endocrine laboratory of the University of Chicago. Given the pulsatility of testosterone secretion driven by periodic oscillations in the hypothalamic gonadotropin-releasing hormone and the luteinizing hormone of the pituitary, pooling of consecutive blood samples provides a more accurate and reproducible assessment of circulating androgen levels.[17,18] Total testosterone was measured by radioimmunoassay using a kit from Diagnostic Products (Los Angeles, CA). The free fraction of circulating testosterone was measured using a flow dialysis technique as previously described.[19] The intra- and inter-assay coefficients of variation were 3.8 and 8.7%, respectively.

Wrist activity monitoring was used to determine the usual amount of nighttime sleep of the study participants in everyday life settings. Data were collected in 1-minute epochs around the clock for a total of 6 to 9 days using an Actiwatch accelerometer (Mini-Mitter, Bend, OR) placed on the wrist of the subject's nondominant hand. Automated analysis of all wrist activity records was performed at the medium sensitivity setting of the software provided with the device (Actiware Sleep software, version 3.4) facilitated by self-reports of individual bed and wake-up times.[20] The usual amount of nighttime sleep of each individual was determined by the average number of epochs scored as sleep across all bedtime periods in his recording.

After completing their home actigraphy monitoring, the volunteers spent 2 consecutive nights with usual bedtimes in the General Clinical Research Center of the University of Chicago. Full polysomnographic monitoring (DigiTrace, Boston, MA) during the first night was used for habituation and to exclude the presence of a primary sleep disorder, such as sleep disordered breathing. Respiratory events were scored according to AASM criteria.[21] For each subject a respiratory disturbance index (RDI) was calculated to reflect the average frequency of documented apnea and hypopnea episodes per hour of sleep. Volunteers with clinically significant sleep disordered breathing, defined as an RDI > 15, were excluded from the study. The analysis of sleep in the laboratory

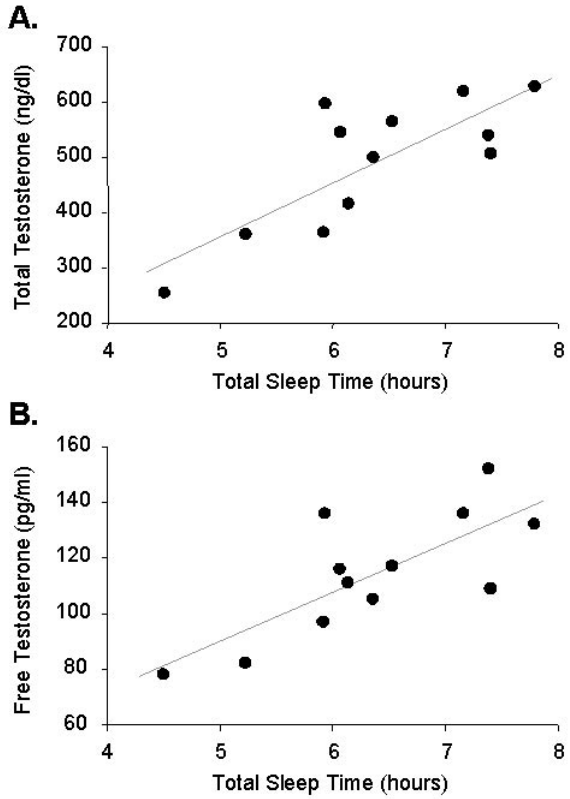

Figure 1—Morning levels of plasma total (a) and free (b) testosterone in healthy older men as a function of the amount of their total nighttime sleep measured by polysomnography. Superimposed best fit lines illustrate the unadjusted bivariate correlation of these variables.

was based on the polysomnographic records obtained during the second night including only EEG, EMG, and EOG data, which were scored in 30-second epochs of wake, movement, stage 1, 2, 3, 4, and rapid eye movement (REM) sleep according to standard clinical criteria.[22] Sleep onset was defined as the timing of the first epoch of stage 2 sleep. Total sleep time was calculated as the sum of all periods after sleep onset scored as stage 1, 2, 3, 4, or REM sleep. Sleep efficiency was calculated as the percent of time in bed that was scored as sleep. Sleep maintenance was calculated as the percent of time between sleep onset and final awakening that was scored as sleep.

Bivariate correlation analysis (SPSS 13.0, SPSS Inc., Chicago, IL) was used to explore the relationship between morning testosterone levels and actigraphic or polysomnographic measures of sleep. Based on these findings and the known effects of aging[1,3] and obesity[2] on circulating androgen levels, TST, age, and body mass index (BMI: equal to the weight of the subject in kilograms divided by his squared height in meters) were simultaneously included in a multiple linear regression model as predictors of morning testosterone levels of the study participants. Since sleep disordered breathing is also known to affect circulating androgen levels[23] and healthy volunteers with RDI < 15 were allowed to enroll in this protocol, additional regression analysis controlling for RDI in addition to age and BMI was also performed. Experimental control of other important biological, behavioral, and clinical confounders (e.g., irregular lifestyle or shift/night work, inadequate nutrition, smoking, excessive alcohol use, medication side effects, and acute and chronic illness including obesity, depres-

Table 1—Clinical, Biochemical, and Laboratory Sleep Characteristics of Study Participants

	Mean	SD	Range
Age (years)	68.9	3.5	64 - 74
Body Mass Index, BMI (kg/m2)	26.4	2.4	22.7 – 29.9
15-item GDS Score	0.5	0.5	0 - 1
MMSE Score	29.9	0.3	29 - 30
Total Testosterone (ng/dl)	491	117	255 - 628
Free Testosterone (pg/ml)	114	22	78 - 152
PSA (ng/ml)	1.2	0.8	0.1 – 3.1
Fasting Blood Glucose (mg/dl)	88	7	76 - 96
Total Cholesterol (mg/dl)	194	25	153 - 241
HDL Cholesterol (mg/dl)	52	13	30 - 68
Triglycerides (mg/dl)	96	44	46 - 206
Bedtime (hr:min)	23:17	1:11	22:01 – 2:02
Wake-up Time (hr:min)	07:07	1:00	6:00 – 9:04
Total Sleep Time (min)	383	58	271 - 469
Sleep Onset Latency (min)	14	9	3 - 32
Sleep Efficiency (%)	81	9	60 - 93
Sleep Maintenance (%)	85	9	61 - 94
Stage 1 Sleep (min)	36	26	11 - 104
Stage 2 Sleep (min)	237	54	97 - 303
Slow Wave Sleep, Stages 3+4 (min)	31	26	1 - 73
REM Sleep (min)	78	25	48 - 130
RDI (events/hour of sleep)	5.9	4.3	0 - 15

PSA: prostate specific antigen; HDL cholesterol: high-density lipoprotein-bound cholesterol (see text for other abbreviations). To convert concentrations of total testosterone from ng/dl to nmol/l multiply by 0.0347, PSA from ng/ml to mcg/l multiply by 1.0, glucose from mg/dl to mmol/l multiply by 0.0555, cholesterol from mg/dl to mmol/l multiply by 0.0259, and triglycerides from mg/dl to mmol/l multiply by 0.0113.

sion, and obstructive sleep apnea) that can alter male androgen levels, was accomplished using the strict screening criteria of the study. In the presentation of the experimental results, statistical significance is assumed when $P < 0.05$, whereas P values between 0.05 and 0.10 are reported as trends.

RESULTS

Selected characteristics of the study participants are summarized in Table 1. There was a considerable degree of between-subject variability in the polysomnographic measures of sleep quantity and quality: research volunteers slept between 271 and 469 min/night in the laboratory, and their sleep efficiency and sleep maintenance varied from 60% to 93% and from 61% to 94%, respectively. Total sleep time in the laboratory correlated well (Pearson's $r = 0.842$, $P = 0.001$) with the average amount of nighttime sleep at home (range 258 to 448 minutes, mean ± SD: 381 ± 51 min/night). Thus, the combined use of objective methods to quantify sleep in healthy older men by polysomnography in the laboratory and by wrist actigraphy at home, demonstrated the presence of large and reproducible between-subject differences in the amount of sleep that they obtain during the night. In contrast, the subjective estimates of the amount of usual nighttime sleep (range 6.0 to 8.5 hours, mean 428 ± 54 min/night) reported by the study participants in response to the PSQI question "During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed)" were not correlated with the amount of sleep recorded in the laboratory ($r = 0.076$, $P = 0.814$) or at home ($r = 0.102$, $P = 0.752$).

Morning levels of total testosterone varied more than 2-fold across subjects: individual values ranged between 255 and 628 ng/dl. Exploratory correlation analysis without adjustment for potential confounders revealed a significant positive association of morning testosterone levels with several polysomnographic measures of nighttime sleep, including total sleep time (TST), the amount of stage 2 and REM sleep, sleep efficiency, and sleep maintenance (Table 2). Among them, TST was the single integrative polysomnographic index with the strongest relation to morning testosterone concentrations (Figure 1). Consistent with this observation, a significant positive correlation between the average amount of nighttime sleep and morning total ($r = 0.757$, $P = 0.004$) and free testosterone levels ($r = 0.653$, $P = 0.021$) was also identified, when 6 to 9 days of wrist actigraphy data were used as an objective measure of habitual sleep at home. In addition, repeatedly positive correlations were found between the morning testosterone levels of the subjects and the amount of their sleep recorded during a single night of wrist actigraphy monitoring at home. For example, the coefficients of correlation between the total testosterone concentrations of the subjects at the beginning of the study and their subsequent nightly sleep times were $r = 0.714$, $r = 0.522$, $r = 0.318$, $r = 0.639$ and $r = 0.539$ for nights 1 through 5, respectively. In contrast, no significant relationship was detected between the morning concentrations of total ($r = 0.047$, $P = 0.884$) or free testosterone ($r = 0.103$, $P = 0.750$) and the usual time of nighttime sleep onset of the subjects (group mean ± SD: 23 h 56 min ± 1 h 29 min by wrist actigraphy). Similarly, there was no significant association between the circulating levels of androgens ($r = 0.138$, $P = 0.669$ for total testosterone, and $r = 0.227$, $P = 0.478$ for free testosterone) and the usual time of morning awakening of the subjects (group mean ± SD: 7 h19 min ± 1 h 34 min by wrist actigraphy).

The results of the multiple regression analysis revealed that TST was a strong independent predictor of morning total and free testosterone levels in healthy older men (Table 3, Model 1). The

Table 2—Pearson's Coefficient of Correlation between Polysomnographic Measures of Sleep and Morning Testosterone Concentrations

	TT	FT	TST	SE	SM	S1	S2	SWS	REM
FT	.856**								
TST	.787**	.761**							
SE	.575	.630*	.878**						
SM	.414	.439	.705*	.871**					
S1	-.222	-.094	-.450	-.647*	-.868**				
S2	.719**	.590*	.855**	.858**	.799**	-.715**			
SWS	-.139	-.046	.122	.316	.499	-.503	.045		
REM	.618*	.610*	.790**	.520	.306	-.049	.511	-.269	
RDI	.146	.091	.171	.006	-.083	.116	.199	-.614*	.394

TT – total testosterone; FT – free testosterone;
TST – total sleep time; SE – sleep efficiency;
SM – sleep maintenance; S1 – amount of stage 1 sleep;
S2 – amount of stage 2 sleep; SWS – amount of slow wave sleep;
REM – amount of rapid eye movement sleep;
RDI – respiratory disturbance index.
** $P < 0.01$; * $P < 0.05$.

Table 3—Summary of Results from Multiple Linear Regression Analyses.

	Total Testosterone				Free Testosterone			
Model 1	**B**	**95 % CI**	**Beta**	**P**	**B**	**95 % CI**	**Beta**	**P**
TST (hours)	97	22 to 172	0.792	0.017	17	2 to 32	0.741	0.029
Age (years)	-8	-23 to 8	-0.234	0.281	-2	-5 to 2	-0.239	0.298
BMI (kg/m^2)	2	-28 to 32	0.038	0.890	-0.02	-6 to 6	-0.002	0.994
Model 2								
TST (hours)	98	20 to 177	0.803	0.021	18	2 to 33	0.756	0.029
Age (years)	-12	-33 to 9	-0.366	0.209	-3	-7 to 1	-0.427	0.156
BMI (kg/m^2)	1	-31 to 32	0.014	0.960	-0.3	-6 to 6	-0.036	0.900
RDI (#/hr)	-6	-23 to 11	-0.214	0.449	-2	-5 to 2	-0.307	0.296
Model 3								
WA-S (hours)	88	21 to 155	0.643	0.017	14	-1 to 29	0.524	0.068
Age (years)	-6	-21 to 10	-0.167	0.440	-1	-5 to 2	-0.191	0.448
BMI (kg/m^2)	-15	-38 to 9	-0.297	0.194	-3	-8 to 2	-0.336	0.206

Model 1: Total testosterone, R^2=0.675, P=0.024; Free testosterone, R^2=0.636, P=0.036.
Model 2: Total testosterone, R^2=0.702, P=0.050; Free testosterone, R^2=0.692, P=0.055.
Model 3: Total testosterone, R^2=0.677, P=0.023; Free testosterone, R^2=0.560, P=0.074.
TST – total sleep time measured by polysomnography; WA-S – average amount of nighttime sleep measured by home wrist actigraphy; BMI – body mass index; RDI – respiratory disturbance index; B – unstandardized regression coefficients; 95% CI – 95% confidence interval for B; Beta – standardized regression coefficients.

inclusion of RDI in the model did not significantly modify the strong association of TST with the morning testosterone levels of the study participants (Table 3, Model 2). Finally, when home wrist actigraphy was used to quantify the usual amount of nighttime sleep in a multiple regression analysis controlling for age and BMI, average sleep time was again a significant independent predictor of the morning total testosterone concentrations of the subjects (Table 3, Model 3).

DISCUSSION

This study indicates that healthy older men exhibit reproducible differences in the amount of nighttime sleep that they obtain either at home or in the laboratory, which may be associated with a substantial part of the variability in their morning testosterone levels. When other important biological, behavioral and clinical confounders were controlled for, the objectively measured amount of nighttime sleep in healthy older men was found to be a significant and independent predictor of their morning total and free testosterone levels.

Studies of healthy young adults have provided important clues about the potential causality of the association between sleep and blood testosterone levels in older men. Several reports indicate that the androgen concentrations in the circulation of young adults decline significantly during periods of total sleep deprivation and recover promptly once the sleep of the subjects is restored.[8-10] In contrast, reversible pharmacological castration of healthy men has been shown to have no effect on the total amount and overall architecture of nighttime sleep.[24] Together with these observations, the results of the present study raise the possibility that human sleep may contribute to the maintenance of circulating androgen levels in older adults. The significant correlation of TST with the polysomnographic stages having the largest contribution to the total amount of sleep (stage 2 and REM), as well as with sleep efficiency and sleep maintenance (see Table 2), suggests that all of these variables measure a common sleep construct related to higher testosterone levels in healthy older men. These results provide experimental support for the theoretical predictions of Axelsson et al,[8] who based on observations in healthy young males noted that sleep was accompanied by an exponential rise in circulating testosterone concentrations.

Since plasma androgen levels decline exponentially with time after awakening,[8] it is possible that the older subjects who slept less also got up earlier in the morning and may have been awake for a longer period of time before their blood samples were taken. However, the lack of significant correlation between measured testosterone levels and the time of sleep onset or morning awakening in the present study supports the primary role of sleep quantity and/or quality for the observed association in older adults. Sleep architecture is commonly affected by the process of aging: it becomes increasingly fragmented by arousals and episodes of awakening, which can result in poor sleep maintenance and consolidation, and a reduction in the overall amount of sleep.[7,13] Emerging evidence now indicates that a similar pattern of partial sleep loss can affect multiple aspects of the mammalian endocrine system, including declines in some anabolic hormones.[25] Since testosterone secretion in healthy young adults is coupled to a stage of deepening sleep,[26] the potential of age-related sleep fragmentation to disrupt the secretion of androgens in older men (with or without loss of overall sleep time) warrants additional investigation.[11]

Measurements in monozygotic and dizygotic pairs of 59- to 70-year-old twins indicate that genetic factors contribute significantly to the phenotypic variation in circulating testosterone levels.[27] In addition to the effects of aging, genetic factors may also play a role in determining the quantity and quality of sleep in older men. For example, human twin studies indicate that sleep quantity is under the influence of genetic factors,[28] while experiments in rodents demonstrate that even single gene mutations can have an effect on the 24-hour amount and distribution of sleep.[29,30] Therefore, the inherited alleles of sleep related genes combined with the impact of aging on the individual sleep phenotype may determine some of the differences in sleep of older men and contribute to the variability in their circulating testosterone levels.

In this broader biological context, the results of the present study raise the possibility that alterations in sleep may represent one of the mechanisms that can transform the process of physiological aging into changes of neuroendocrine function in older adults.

The present study has several strengths and limitations. First, the experimental design included laboratory polysomnography in addition to home actigraphy in order to screen for sleep disorders and to obtain 2 sets of objective indices of inter-individual sleep variability in older men. This was crucial for the results of this study, since the sleep time of the subjects documented by self-report did not correlate with the objectively measured amount of sleep and showed no association with their morning testosterone levels. Second, in an attempt to mimic everyday clinical practice, all testosterone samples were obtained after a night of usual sleep at home and prior to the collection of any sleep or other data for this study. This made it possible to avoid the confounding effects of stress associated with inpatient sleep recording and overnight blood sampling on circulating androgen levels. For example, using simultaneous laboratory monitoring of both sleep and androgen levels in healthy men between the ages of 45 to 75 years, Schiavi et al[23] found only a modest association between sleep efficiency and overnight testosterone concentrations, which lead them to suggest that changes in sleep architecture may be related to alterations in the activity of the gonadal axis of older individuals. By focusing on a more homogeneous group of 64- to 74-year old men without sleep apnea and minimizing study-related sleep disruption, the present data indicate that there is a much more robust correlation between the amount of sleep obtained by older men during the night (either at home or in the laboratory) and their morning testosterone levels.

The decision to monitor sleep after all blood samples for androgens have been drawn can also be viewed as one of the limitations of this study. Indeed, the above discussion of the results is based on the assumption that the pattern of between-subject variability of sleep during the night prior to the morning blood sampling for testosterone matched the individual differences in sleep quantity and quality documented on subsequent monitoring. The validity of this assumption in the present study is supported by the following observations: 1) all subjects reported that their sleep was of usual quantity and quality during the night prior to the morning blood sampling; 2) the pattern of between-subject variability in the amount of nighttime sleep was stable and well reproducible when home actigraphy and laboratory polysomnography were used consecutively on 2 different occasions ($r = 0.842$, $P = 0.001$); and 3) consistently positive correlations were found between the testosterone levels of the subjects at the beginning of the study and the individual amounts of sleep recorded on any single night of home actigraphy.

The conclusions of this study may also be limited by the inclusion only of a small group of healthy older men who met the strict screening criteria and were willing to undergo 2 nights of laboratory sleep monitoring. Since this carefully selected convenience sample may not be representative of the larger population of healthy older men in the community, the best use of the reported results will be as guidance for the development of larger field-based studies. Nevertheless, the presence of significant inter-individual variability in the amount of nighttime sleep and circulating testosterone levels in this rigorously screened group of healthy older men supports the biological significance of the reported results.

In its report, the Institute of Medicine Committee on Assessing the Need for Clinical Trials of Testosterone Replacement Therapy did not find sufficient evidence that testosterone treatment benefits healthy older men.[31] In addition, one of the Committee's recommendations was that additional research should focus on defining how and why testosterone levels decrease with age and identifying reversible factors that may prevent the age-related decline without the need for testosterone supplementation.[4,31] From a clinical perspective, inter-individual differences between 4.5 and 7.5 hours of sleep per night in this study correspond to a range of total testosterone concentrations beginning at around 200-300 ng/dl considered to be borderline-low for older men, and reaching 500-700 ng/dl, which represent mid-normal values commonly seen in healthy young adults (Figure 1).[32] The detailed understanding of the biological significance and clinical implications of the variable androgen decline in older men[5] may, therefore, benefit from additional studies addressing the role of sleep and its age-related changes in this process. For the time being, these findings suggest that complaints of poor or insufficient sleep in otherwise healthy older men can be associated with a more pronounced age-related androgen decline. Eliciting such sleep complaints in the physician's office may facilitate the judicious interpretation of lower testosterone levels in the older male patient.[32]

ACKNOWLEDGMENTS

This work was supported by a grant from the American Federation for Aging Research. The University of Chicago General Clinical Research Center is supported by NIH grant MO1-RR00055. A. Nedeltcheva, C. Smiley, and J. Imperial provided expert technical assistance with the study protocol. E. Van Cauter offered helpful comments on the initial draft of this manuscript.

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