

Sleep, sex steroid hormones, sexual activities and aging in Asian men

Short Title: Sleep, sex steroids and sexual activities in men

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ABSTRACT

This was a cross-sectional study to examine the different association of age and sleep duration with sex steroid hormones and sexual activities in 531 Asian Chinese men aged between 29 y and 72 y old. **Methods:** Sleep duration and sexual activities were evaluated through a self-administered questionnaire, while total testosterone (T), sex hormone binding globulin (SHBG), estradiol (E2) and dehydroepiandrosterone sulphate (DHEAS) were measured by established immunoassay methods in a single blood sample collected between 8.00am and 11.00am. Bioavailable testosterone (BioT) was calculated using the Vermeulen's formula. **Results:** Age was a major determinant of sleep, sex steroid hormones and sexual activities in men. BioT, DHEAS, coital frequency (CoitalF), masturbation and sleep duration (SlpD) declined with age. On the other hand, SHBG and E2 increased with age. Sleep duration, independent of age, aerobic exercise and body fat was positively associated with T and BioT, but not with DHEAS and E2 or any of the sexual activities studied. Men who masturbated had higher levels of both T and BioT. DHEAS was significantly associated with coital frequency and desire for sex. **Conclusion:** The present study showed that besides age, sleep duration was associated with androgen concentrations in men and thus the evaluation of the sleep hygiene may be beneficial in the management of men with low androgen concentrations. DHEAS may be independently associated with some sexual functions in men.

Key words: *Physical exercise, aging, Asian men, sexual activities, testosterone, Bioavailable-T, DHEAS*

INTRODUCTION

Circulating sex steroid hormone concentrations changed with age in men with wide inter-individual variability among different study groups (Mohr et al, 2005; Feldman et al, 2002; Harman et al, 2001; Orwoll et al, 2006; Ferrini and Barrett-Connor, 1998; Morley et al, 1997; Goh et al, 2007). In addition, sex steroid hormone concentrations were significantly associated with several lifestyle factors including sleep and exercise (Goh et al, 2007; Ponzolzer et al, 2005). However, it is unclear whether changes in sex steroid hormone concentrations associated with aging were due purely to aging or in combination with some lifestyle factors. Unraveling the differential associations of aging and lifestyle factors on sex steroid hormone concentrations may have some clinical significance, as low sex steroid hormone concentrations have been associated with adverse effects on cognition, sexual functions, bone and body composition, glucose

metabolism and quality of life (Lu et al, 2006; Nagatell et al, 1994; Villareal, Holloszy and Kohrt, 2000; Kaufman and Vermeulen, 2005; Stellato et al, 2000).

The widespread participation in internet activities and globalized cross-time zone trading may have compromised the normal circadian sleep in many people. Chronic sleep restriction has become one of the most common and yet least studied health issues. It is endemic in modern society. Americans are sleeping less than the recommended 8h per night (Bliwise et al, 1992; Harrison and Horne, 1995; National Sleep Foundation). We have reported that sleep duration decreased with age (Goh et al, 2007) and disrupted sleep can affect androgen concentrations (Penev, 2007), but the reported association between sleep and androgen concentrations has been equivocal. The reasons, in part, may be due to study involving small number of subjects, and studies being carried out in laboratory or operational settings as in intensive military training (Penev, 2007; Opstad, 1992; Remes, Kuoppasalmi and Adlercreutz, 1985). The impact of sleep on androgen concentrations under these settings may not necessarily represent that of men living in the community. The present study sought to evaluate the association of age and sleep duration with sex steroid hormone concentrations and sexual activities in a group of men living in the community.

MATERIALS AND METHODS

Subjects

This study was approved by the Institutional Review Board of the National University Hospital and each volunteer had given his written informed consent. The method was previously reported in an early analysis (Goh et al, 2007). Five hundred and thirty-one Singaporean Chinese men, aged between 29y and 72y, were included in the analyses. Subjects were recruited from the general public through an open invitation, first through an announcement during the World Congress in Sexology held in Singapore. The announcement was carried in the major newspapers in Singapore. Continual recruitment was assisted through word of mouth from volunteer to volunteer. The targeted number of men between the ages of 30y to 70y was 400. The good response from the public was, in part, due to the prevailing awareness of the aging issues in Singapore at that time. As the primary objective was to evaluate the determinants of the natural aging process, only subjects with no known existing or history of major medical illnesses such as cancer, hypertension, thyroid dysfunction, diabetes, osteoporotic fracture and cardiovascular events as well as major sleep disorders including sleep apnea requiring chronic treatment were included in the study. None of the subject had a history of erectile dysfunction requiring

treatment. On physical examination, none had genital abnormalities. Subjects were not paid for participation. They represented the diverse spectrum of the Chinese in Singapore, ranging from those with low to high levels of education, working and non-working men (retirees), and those in various types of vocations (Goh et al, 2007). Their profiles were typical in Singapore, which is a highly urbanized city-state with no rural population. Each subject answered a self-administered and investigator-guided questionnaire. Questions asked covered their medical, dietary, social, sex, and family histories and other relevant histories regarding consumption of hormones, supplements and medication, types of beverages, smoking and alcohol consumption.

Methodologies

The self-administered, investigator-guided questionnaire has not been validated, but contained questions that could be categorized. In this questionnaire, subjects were asked to score their average sleep duration per night as well as some common sexual activities listed below over the last 6 months.

<u>Sleep duration per night (SlpD)</u>	<u>Score</u>
• <4h	1
• 4 – 6h	2
• 6 - 8h	3
• >8h	4

Sexual Activities

- a. How many times do you have coitus each month? (CoitalF) _____/month
- b. Are you satisfied with your coital frequency? (DesiredSex)
 - No, I want more sex 1
 - Yes, I am happy with my coital frequency 2
 - No, I want less frequent sex 3
- c. Do you masturbate? (Masturbate)
 - No 1
 - Yes 2
- d. If yes, how many times per month? (No.Times) _____/month

Hormonal assays for total testosterone, SHBG and DHEAS

Hormone concentrations were measured in serum from a single blood sample collected after an 12 h overnight fast between 8.00am to 11.00am. Serum T and E2 concentrations were measured

using reagents and methods recommended by the World Health Organization Matched Reagent Program (Sufi, Donalson and Jeffcoate, 1992) with modification to the scintillation proximity methods established in-house (Goh et al, 1992). The lower limit of quantitation for E2 was 10pg/ml and the inter-assay coefficient of variation ranged from 5 -10% (Goh et al, 1978). T, SHBG and DHEAS were measured using methods reported earlier (Chia, Goh and Ong, 1997). The inter-assay coefficients of variation were for T and DHEAS were less than 10% over the effective concentration ranges and less than 15% for SHBG (Chia, Goh and Ong, 1997).

Method of calculation of BioT

Bioavailable testosterone was calculated using the computer formula of Vermeulen which is available on the ISSAM website. Total testosterone was computed as ng/dL while that for SHBG as nmol/L. Albumin level was assumed to be 4.4g/dL. Hence, BioT was expressed ng/dL (Vermeulen, Verdonck and Kaufman, 1999).

Statistical analysis

Statistical analyses were performed using SPSS for windows version 16.0. Basic descriptive statistics, as well as comparison of means using One-way ANOVA and the Univariate analyses of the General Linear Model coupled with the Least Significant Difference (LSD) as the Post-Hoc test for multiple means were used on continuous measurements and where appropriate. For the non-continuous measurements such as number of men who masturbated, sleep duration, and desire for sex, Chi-squared analyses were used.

Every man had a whole body fat scan using the DEXA (Goh et al, 2007), therefore the total body fat based on the Siri formula from the DEXA machine was used as the index for total body fat . This is preferred over the conventional use of BMI as an index of total body fat.

Most of the continuous measurements such as the sex steroid hormones, coital frequency, body fat were not normally distributed. Hence, they were \log_{10} -transformed before being subjected to the appropriate statistical analyses.

Comparisons of means of various parameters were based of 4 age groups, $\leq 40y$, 41-50y, 51-60y and $>60y$ as well as on the 4 sleep duration groups: $<4h$, 4-6h, 6-8h and $>8h$, 2 groups of those who did and did not masturbate, and 3 groups of desire for sex: want more, happy and want less sex.

Since age was a major determinant, the General Linear Model Univariate procedure provided regression analysis and analysis of variance for one dependent variable by one or more factors and/or variables with age as the covariate. In other analyses, age, body fat and aerobic exercise scores (AeroS) (Goh et al, 2007) were evaluated as covariates with the corresponding values for age and body fat and AeroS set at the respective values shown in each table. Since sleep duration was not a continuous measurement, the regression was weighted for sleep duration. The alpha was set at 0.05.

Age, sleep duration and AeroS have significant interactions. In regression analysis for total T, with sleep duration, age, body fat and AeroS as covariates, the collinearity statistics and diagnostics using tolerance, variance inflation factor (VIF), eigen value, and condition index, showed that there was no collinearity problem for sleep duration with the other three covariates and the correlation noted for sleep duration with T and BioT could be explained mainly by sleep duration.

RESULTS

Except for T and desire for sex, all other sex steroid hormone concentrations and sexual activities as well as sleep duration changed significantly with age (Table 1). Even when the analyses of T with age groups were done with body fat, exercise scores as covariate, and weighted for sleep duration, there were no significant differences in T among all 4 age groups. Among the sex steroid concentrations, the decline of serum DHEAS with age was most dramatic, declining by 11.2%, 28.8% and 42.4%, respectively, in men 41-50y, 51-60y and >60y as compared to the mean concentrations in men less than 40y old (Table 1). Bioavailable testosterone declined by 16.5% to 17.9% in men above 50y when compared to men less than 40y old (Table 1). On the other hand, SHBG in men older than 50y increased by 16.0% to 26.2% when compared to younger men (<40y) (Table 1). Serum E2 concentrations were significantly higher in men above 50y old when compared with men \leq 40y (Table 1). It is noted that the E2 assay used has a sensitivity of down to 10pg/ml which might probably be higher than the lower range of normal men. However, with a precision of up to 10%, the absolute values of the concentrations may not be accurate, however, the observed differences between groups may still be valid.

Eighty-eight percent of men were married and have stable relationship, while 0.6% were living with a partner of the opposite sex; 2.3% were divorced or separated, 1.1% widowed and 7.9% were single. Coital frequency and the number of times that men were engaged in self-

masturbation were reduced by 49.3% and 39.3%, respectively, in men above 60y old when compared to men less than 40y old (Table 1). Similarly, fewer men engaged in self-masturbation in the older compared to the younger age groups (Table 1). There were significantly more men older than 51y who slept less as compared to younger men (<40y old). More than 22% of men older than 50y routinely slept less than 6h nightly as compared to only 8.3% of men younger than 40y (Table 1).

Since age was associated with body fat (DEXA) and aerobic exercise scores and BioT, while T was associated with body fat (DEXA) and aerobic exercise scores, the associations of sleep duration with T and BioT were analyzed with age, total body fat (DEXA) and aerobic exercise scores as covariates. These regression analyses showed that sleep duration, independent of these covariates, was significantly and positively associated with androgen levels (Figure 1). Men who slept between 4h to 6 h and less than 4h, had both T and BioT levels that were, respectively >14% and >35% lower as compared to men who routinely slept more than 8h (Figure 1).

No significant association between sleep duration and DHEAS and SHBG was noted. Likewise, sleep duration was not significantly associated with any of the sexual activities surveyed.

Sexual activities were variably associated with different androgens. Men who engaged in self-masturbation had significantly higher concentrations of both T and BioT, but not DHEAS as compared to those who did not masturbate (Table 2). Those who did masturbate had significantly lower coital frequency than those who did not masturbate (Table 2). On the other hand, DHEAS concentrations were higher in men who were either happy with their coital frequency or who wanted more as compared to those who wanted less sex (Table 3). In addition, DHEAS concentrations were positively associated with coital frequency (beta value = 0.142 and p=0.005).

DISCUSSION

The present study suggests that age is a major determinant of many of the physiological parameters including sleep, sex steroid hormones and sexual activities. As with earlier studies, there were significant declines of DHEAS and BioT, but not T in men as they age (Mohr et al, 2005; Feldman et al, 2002; Harman et al, 2001; Orwoll et al, 2006; Ferrini and Barrett-Connor, 1998; Morley et al, 1997; Goh et al, 2007; Stellato et al, 2000). Both SHBG and E2 were significantly higher in older men as compared to younger men. Significantly more men above 50y

old slept less than 6h nightly as compared to younger men (<40y old). Men above 60y had significantly lower coital frequency, fewer older men wanted more sex than they were already having and fewer older men were engaged in masturbation and if they did, less frequently than younger men.

The present study clearly showed a positive association between habitual sleep duration and androgen concentrations which is independent of age, total body fat, and exercise intensity. Men with acute sleep restriction (those who slept <4h daily) and those with moderate sleep restriction (those who slept between 4 - 6h daily) had significantly lower androgen concentrations (T and BioT), by >35% and >14%, respectively, when compared to corresponding concentrations in men who slept more than 8h. This is one of the first studies that showed a positive association between sleep duration and androgen concentrations in men living in community rather than in men studied under experimental laboratory or military exercise settings as was reported in earlier studies (Penev, 2007; Opstad, 1992; Remes, Kuoppasalmi and Adlercreutz, 1985). It must be noted that there were only 14 men who reported that they routinely sleep for less than 4h. It is unlikely that there will be much more individuals who would routinely sleep less than 4h, as this sleep duration represents chronic severe sleep restriction. However, the fact that T and BioT were significantly lower in men who slept for between 4-6h than those who slept for >6h give credence to the suggestion that men who sleep less than 6h had lower T and BioT than those who sleep more than 6h, even if we were to discount results of those who slept <4h. In addition, sex steroids were measured in a single morning sample from each subject. This represented a weakness of the present study. More accurate estimates of T concentrations would have been achieved if repeat sampling has been employed. Therefore, results of the present study must be viewed with these limitations in mind.

Many today have disrupted circadian sleep pattern, with some sleeping in the day and working in the night, while others having chronic sleep restriction, that is, shortened sleep duration each day. Chronic sleep restriction can affect somatic and emotional well being (Belenky et al, 2003), but relatively little is known of its long term effect on health. Data of the present study indicated that sleep restriction is associated with reduced androgen concentrations and consequently may affect androgen-dependent functions.

A clear association between sleep and androgen concentrations may have significant implications in the management of aging in men and men with late onset hypogonadism (LOH). Therefore, in

their management, apart from looking at other confounding factors including obesity, diabetes and aging (Giagulli, Kaufman and Vermeulen, 1994; Semple, Gray and Beastall, 1988; Gooran, 1996; Wandell and Brorsson, 2000), sleep history of men must be explored as a possible contributing factor for their low androgen concentrations. In men with low concentrations of androgens concurrent with poor sleep habit; the promotion of better sleep hygiene may represent a non-drug intervention for improving their androgen concentrations. However, several pertinent questions concerning the relationship between sleep and androgen concentrations remain to be answered in future research studies. Clarification is needed on whether restoring adequate sleep in men with poor sleep could increase their androgen concentrations. And if it does, how long after restoration of sleep will androgen concentrations be improved? Is the quality of sleep a significant factor in the relationship between sleep and androgen concentrations?

The full extent of the effects of lowered concentrations of androgens cannot be inferred from the current data set, however, it was shown that men with lower concentrations of T and BioT were less likely to engage in self-masturbation. On the other hand, both T and BioT were not associated with coital frequency and desire for more frequent coitus than they were having. Similar observations were noted in earlier studies where weight loss-associated increases in androgen concentrations did not result in changes in sexual function scores, neither were coital frequency and libido associated with T concentrations in aging men (Kaukua, et al, 2000; Sadowsky et al, 1993). In a meta-analysis it was suggested that T treatment of men with low T had only moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercours, scores of erectile function, and overall sexual satisfaction (Isidori et al, 2005). These observations suggest that androgens may have limited sexual motivational effect in men. As noted in the present study, sexual functions were associated with age and other sex steroids, hence, some of the differences noted in the various studies might arise, in part, when age and other factors were not taken into consideration in the analyses.

The positive association between DHEAS and coital frequency in men was independent of age, and men with higher concentrations of DHEAS were associated with a desire for more frequent sex than they were already having. Similar observations were noted by other investigators. Decreased DHEAS was noted in men with orgasmic dysfunction (IIEF II), dysfunction of sexual desire (IIEF III) and decreased sexual function scores (Kuba et al, 2006; Ponholzer et al, 2002). Men treated with DHEAS had improved sexual functions (Adimoelja and Adaikan, 1997). Therefore, it appears that DHEAS may have a more significant role in some of sexual functions

than had been currently suggested. DHEAS is present in similar quantum in men and women and declines dramatically with age. As with men, low concentrations of DHEAS, has been associated with low libido, and sexual dysfunction in women (News-medical.Net; Gracia, et al, 2006). Hence, it is possible that DHEAS might be a common factor modulating sexual functions in both men and women.

Significantly more men older than 60y had sleep duration of less than 6h nightly when compared to younger men (<40y). This observation supports the common notion that men tend to sleep for shorter duration as they age. An adequate nightly sleep is a key component of man's recuperation process following a day's work. This recuperation process is the engine for the regeneration of alertness required for optimal cognitive and physical functional capacities (Penev, 2007). Generally, adequate sleep duration enhances alertness and performance during subsequent wakefulness (Opstad, 1992; Remes Kuoppasalmi and Adlercreutz, 1985). In the present study, the observation that total T and BioT were highest in men who slept between 6h to 8h or more gives indirect support to the suggestion by Belenky that the optimal sleep duration is about 8h (Belenky et al, 2003).

Several sexual activities declined with age. Coital frequency in Singaporean men decreased from an average of 4.46 times per month in men ≤ 40 y old to 2.26 times in men over 60y old. The observed coital frequencies as compared to many other countries were low and concurred with the 2005 Durex sex survey which ranked Singapore second lowest besides Japan among more than 100 countries surveyed. In contrast to Greece which had annual frequency of sex of 138, those for Singapore and Japan were 73 and 45, respectively (Durex's Global Sex Survey, 2005). Although the coital frequencies of Singaporean men, by any account, were low, they should not be interpreted as an indication of sexual dysfunction. Coital frequency and sex must be viewed within the cultural context of the population. In some cultures, sex may be higher in the priority list than in another culture. Singapore is a highly urbanized and competitive society. Men tend to spend most of his energy on career and family. This suggestion is supported by our earlier study which noted that most men and women reported that they were happy with their coital frequency (Goh et al, 2004). Interestingly, men with higher coital frequency did not desire for more sex and were less likely to engage in masturbation. Those with lower coital frequency might have unmet sexual desire and in some, this desire was met by engaging in masturbation.

In summary, the present study shows that age remains a major determinant for many

physiological parameters including sleep, sex steroids, and sexual activities. As men age, significant declines in sleep duration, BioT and DHEAS concentrations, coital frequency, engagement in masturbation, and frequency of masturbation were noted. Independent of age, body fat, and exercise intensity, sleep duration was positively associated with both T and BioT concentrations. The average coital frequency in Singaporean men was low. Testosterone and BioT were positively associated with masturbation but not with coital frequency. On the other hand, DHEAS was associated with coital frequency in men. In addition, DHEAS was associated with men's desire for more sex, signifying possibly a role of DHEAS in sexual functions. The significant association of sleep with androgen concentrations suggests that sleep might be a contributing factor in the etiology of men with low concentrations of androgen. Therefore, in the management of men with low androgen concentrations, an evaluation of their sleep hygiene might add to the understanding the etiology of their hypogonadal state.

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Figure and Table Legends

Table 1: Association of age with steroid hormone levels and sexual activities in men

Note: # = geometric means and the 95% confidence intervals for mean
@ = total T concentrations in the 4 age groups were not significantly different from each other.

* = Chi squares analyses were used to evaluate the differences between groups
a= levels were significantly different from those in Gps 2, 3 & 4 ($p < 0.05$)
b = Levels were significantly different from those in Gps 2 & 3 ($p < 0.05$)
c= Levels were significantly different from those in Gps 3 & 4 ($p < 0.05$)
d = Levels were significantly different from those in Gp 3 ($p < 0.05$)
e= Levels were significantly different from those in Gp 4 ($p < 0.05$)

Table 2: Geometric means and 95% confident intervals for mean of T and BioT & coital frequency in men who did not or were engaged in masturbation

Note: The covariates appearing in the model were evaluated at the following values age = 50.3y and percent body fat = 17.0%, Aerobic exercise score = 3.15 and the regression were weighted for sleep duration

a= levels were significantly lower than those in Gp 2 ($p = 0.003$)
b= levels were significantly lower than those in Gp 2 ($p = 0.022$)
c= levels were significantly lower than those in Gp 2 ($p = 0.001$)

Table 3: Geometric mean and the 95% confident intervals for mean of DHEAS and coital frequency in men with different desires for sex.

Note: The covariates appearing in the model were evaluated at the following values age = 50.0y, percent body fat = 17.2, aerobic exercise score = 2.98 and the regression was weighted for sleep duration

a= levels were significantly higher than those in Gps 2 & 3 ($p = 0.025, & 0.009$)
b = levels were significantly lower than in Gp2, but higher than in Gp3 ($p = 0.033, & 0.009$)
c = levels were significantly higher than in Gp3 ($p = 0.005$)

Figure 1: The boxes represent the mean and bar +SD of T (checkered boxes) and BioT (dotted boxes) in men in the different sleep duration groups.

Note: The covariates appearing in the model were evaluated at the following values age = 50.3y and body fat = 17.0%, aerobic exercise score = 3.11.

a= T levels were significantly lower than Gps 2, 3 & 4 ($p = 0.042, 0.007 & 0.002$)
b = T levels were significantly lower than Gp4 ($p = 0.026$)
c = BioT levels were significantly lower than Gps 3 & 4 ($p = 0.015 & 0.005$)
d = BioT levels were significantly lower Gps 3 & 4 ($p = 0.039 & 0.009$)

Table 1

Age groups (n) Parameters	Gp1 (71) (<40y)	Gp2 (200) (41-50y)	Gp3 (179) (51-60y)	Gp4 (81) (>60y)
Total T (ng/dL)#	507@ 467-552	489@ 465-514	468@ 444-493	508@ 470-550
SHBG (nmol/L)#	25.6 ^c 23.6-27.6	26.2 ^c 24.9-27.5	29.7 28.2-31.4	32.2 29.8-34.8
BioT (ng/dl)#	285 ^c 261-311	267 ^c 254-281	234 221-249	238 217-261
DHEAS (ng/ml)#	2795 ^a 2513-3110	2482 ^a 2332-2642	1990 ^a 1846-2144	1611 1453-1786
E2 (pg/ml)#	26.8 ^a 23.9-30.1	30.8 29.0-32.8	32.9 30.9-35.0	31.1 28.3-34.2
Total body fat by DEXA#	15.6 ^b 14.1-17.2	17.1 16.4-17.8	17.9 ^e 17.2-18.7	16.2 15.0-17.6
Coital frequency/month#	4.46 ^c 3.64-5.46	3.99 ^c 3.62-4.40	3.35 ^e 3.02-3.73	2.26 1.88-2.72
% n who want more sex*	22.9% ^e	29.1% ^e	30.5%	21.2%
% who masturbate*	51.8 ^a	34.6 ^d	23.3	32.8
Mast. No. times/mth	3.05 ^e 2.15-4.32	2.28 1.95-2.67	2.34 1.94-2.83	1.85 1.41-2.42
% who slept <6h*	8.3 ^c	12.4 ^c	22.9	26.9

Table 2

Masturbation groups (n) Parameters	Gp1 (322) Did not masturbate	Gp2 (155) Masturbated
T (ng/dL)	470 ^a 453-488	537 508-569
BioT (ng/dL)	245 ^b 236-255	279 262-296
Coital frequency/month	3.87 ^c 3.61-4.16	2.94 2.62-3.29

Table 3

Desire for sex (n) Parameters	Gp1 (119) Want more sex	Gp2 (290) Happy with rate	Gp3 (17) Want less sex
DHEAS (ng/ml)	2410 ^a 2213-2630	2143 2028-2265	1706 1334-2183
Coital frequency	3.22 ^b 2.85-3.64	3.76 ^c 3.49-4.06	2.03 1.47-2.81

Figure 1

