The Aging Male, December 2006; 9(4): 207–213

informa
healthcare

Age related variation of salivary testosterone values in healthy Japanese males

AKIKO UCHIDA[1], RICHARD G. BRIBIESCAS[2], PETER T. ELLISON[3], MASAO KANAMORI[4], JUKO ANDO[5], NOBUYOSHI HIROSE[6], & YUTAKA ONO[7]

[1]*School of International Liberal Studies, Waseda University, Japan,* [2]*Department of Anthropology, Yale University, USA,* [3]*Department of Anthropology, Harvard University, USA,* [4]*Biwako Seikei Sport College, Japan,* [5]*Faculty of Letters, Keio University, Japan,* [6]*School of Medicine, Keio University, Japan, and* [7]*Health Center, Keio University, Japan*

(Received 29 April 2006; accepted 10 October 2006)

Abstract

Objective. We examined age associated variation in salivary testosterone values among Japanese males as well as anthropometric measurements.

Methods. Salivary samples were collected in pretreated sodium azide treated tubes. The first series: 15–79-year-old males ($n = 99$); two morning and two evening samples were collected at home for two days. The second series: 90-year-old males ($n = 29$); one morning sample was collected. Testosterone values were determined using an iodine125-based radio-immunoassay kit modified for saliva.

Results. Results show 1) a significant decrease in salivary testosterone values from 20s to 40s and older, 2) no significant decline after 40 through 90 years old, 3) no significant age-related differences in the degree of intraindividual diurnal fluctuation across age groups of 40–70s, and 4) higher BMI is associated with the lower salivary testosterone among 40–70s.

Conclusions. These results suggest that neither a constant decrease of salivary testosterone values or markedly reduced intraindividual fluctations are universal aspects of aging. Older males may maintain relatively high testosterone levels compared to younger men and a relatively 'robust' neuroendocrinological system.

Keywords: *Aging, testosterone, Japanese males, variation*

Introduction

Age-related declines in serum total, free, and salivary testosterone levels in western populations have been reported by both cross-sectional and longitudinal analyses [1–7]. However we now know there are significant differences in aging patterns of male salivary testosterone values between populations. Some groups in developing countries exhibit significantly lower salivary testosterone levels compared to industrialized western populations as well as more attenuated age related declines [7–12]. Campbell et al. [11,12] reported some differences in aging patterns in association with different life styles among male Kenyan pastorals. Among Asian populations, patterns of age related decline of male testosterone are variable depending on the measure used (serum total testosterone, serum free testosterone), and on the age ranges in question [13–17].

Inter and intraindividual testosterone variation is also associated with illness severity [2,18] and body composition such as amount of skeletal muscle [19–21], as well as adipose tissue deposition and distribution [22–26]. Males with depressive mood also tend to show lower testosterone levels [27]. These results suggest that the commonly reported decline of testosterone values after the third decade of life observed in western countries may not be caused by aging per se. Instead, any association between testosterone and age may be a result of various factors, including energy availability and utilization during maturation, body composition, as well as age-related life style or illness [7,11,30,31].

Another aspect of male testosterone variation with aging in western countries is loss of intraindividual variation. Morning values tend to be lower, and thus similar to evening values in older men. Bremner et al. [32] reported that the difference in testosterone levels between groups of young and older men was significant only during the morning (4 am to 12 am). Considering the marked variation in testosterone values and aging patterns across populations, the universality of deterioration of pulsatile endocrinological activity with age may also need to be reexamined.

Japanese male life expectancy is 78.6 years old, longer than most industrialized countries [33,34]. On the other hand, probably due to the spread of westernized life styles, prostate cancer mortality has

Correspondence: Akiko Uchida, School of International Liberal Studies, Waseda University, 1-21-1, Nishi-Waseda, Shinjuku-ku, Tokyo 169-0051, Japan. Tel: 81-3-3203-9799. Fax: 81-3-3208-8401. E-mail: a.uchida@waseda.jp

ISSN 1368-5538 print/ISSN 1473-0790 online
DOI: 10.1080/13685530601060461

been rising dramatically, approaching the level of western countries during the past 40 years in Japan [35]. In light of the emerging data on population variation in male testosterone, Japanese populations present a germane set of circumstances that make them of substantial interest to human biologists and clinicians interested in senescence and reproductive function. This study reports variation in salivary testosterone values and the aging pattern of healthy Japanese males. These results along with those from other Asian populations provide useful information for the better understanding of endocrinological associations with senescence, and also speak to the appropriate clinical applications of steroid hormones, including the growing trend of androgen supplementation.

Methods

Subjects were healthy community living urban and suburban Japanese males. Two series of sample collection were conducted. Salivary samples were collected according to the protocols of Lipson and Ellison [36]. The subjects of the first series (15–79 years old, total $n = 99$) provided two morning (AM) and two evening (PM) saliva samples that were collected at home over two days in pretreated sodium azide treated tubes. The subjects of the second series (90 years old, $n = 29$) provided one morning sample at our study site at Kakegawa City.

Collected saliva samples were analysed at the Reproductive Ecology Laboratory within the Department of Anthropology at Yale University. Testosterone values were determined for each sample using an iodine125-based radioimmunoassay kit modified for saliva, developed by the Reproductive Ecology Laboratory at Harvard University (Catalogue #DSL-4100, DSL Laboratories, Webster, TX, USA). Inter-assay variation as determined by high and low quality control pools were 17.2% and 22.7%, respectively. Intra-assay variation was 3.9%. Blanks consistently read below detection limits. Body mass index (BMI) was determined using the standard formula of weight (kg)/height $(m)^2$.

The differences between groups were tested by two-tailed t-test and Scheffe's test after log-transformation of the salivary testosterone values. Associations between diurnal variation in testosterone and related variables were conducted using linear regression. The Yale Committee for the Protection of Human Subjects approved this investigation.

Results

First, the general aging pattern of salivary testosterone variation was analysed by comparing seven age groups. The two AM and PM values were averaged separately within each subject of the first sample series (15–79 years old). Table I shows the basic statistics of AM and PM salivary testosterone, as well as BMI. The 20s group showed the highest average testosterone value. There was a significant decline between the AM testosterone values of 20s and 40s onward ($p < 0.01$) (Figure 1). However, after 40s there was no significant decrease through the 90s in the AM testosterone values. Although there was some decrease in PM testosterone values after 30s, the difference was not significant.

While middle-aged and older Japanese males (40–70s) did not show marked age-related decline in testosterone values, this age group showed an association between BMI and salivary AM testosterone values. The AM testosterone of the low-BMI (<22.5) group was significantly higher than the high-BMI (>25.5) group (Figure 2, $p < 0.05$). There was no significant correlation between BMI and AM-Tsal among 30s or younger groups.

Intraindividual diurnal fluctuation was represented by the difference between the lowest and the highest testosterone value among the four samples within each subject. The averages of diurnal fluctuation were higher for the young groups compared with those of 40 and older. However, because within group variation is so marked, the degree of fluctuation is not significantly different between the age groups (Table II). The correlation between the highest values and the range of intraindividual fluctuation was high ($r = 0.86$) (Figure 3). Those with high morning

Table I. Sample number for each age group, average ages, and average testosterone values by age-group.

Age group (n)	Age Mean ± SD	AM-Tsal (pmol/L)*1 Mean ± SD	PM-Tsal (pmol/L)*1 Mean ± SD	BMI Mean ± SD
15–19 (18)	16.6 ± 0.86	348.6 ± 141.3	150.6 ± 88.8	21.5 ± 4.47
20s (16)	22.9 ± 2.5	441.5 ± 240.6*2	240.9 ± 122.8*3	22.9 ± 2.74
30s (12)	36.4 ± 2.4	387.3 ± 321.9	180.8 ± 156.7	25.1 ± 3.35
40 & 50s (18)	48.2 ± 5.5	273.5 ± 170.4	179.2 ± 137.0	24.4 ± 3.81
60s (22)	64.5 ± 8.0	237.5 ± 178.6	129.4 ± 86.5	24.3 ± 2.39
70s (13)	72.1 ± 3.5	223.7 ± 173.3	113.1 ± 75.8	24.4 ± 3.53
90s (29)	90	227.4 ± 152.7		

AM-Tsal: morning salivary testosterone; PM-Tsal: evening salivary testosterone; BMI: Body Mass Index; SD: Standard Deviation. *1: Two samples were averaged per individual. *2: After log transformation significantly different from 40 & 50s and older ($p < 0.01$, t-test and Scheffe's test). *3: After log transformation significantly different from 60s and 70s ($p < 0.01$, t-test; n.s. Scheffes test).

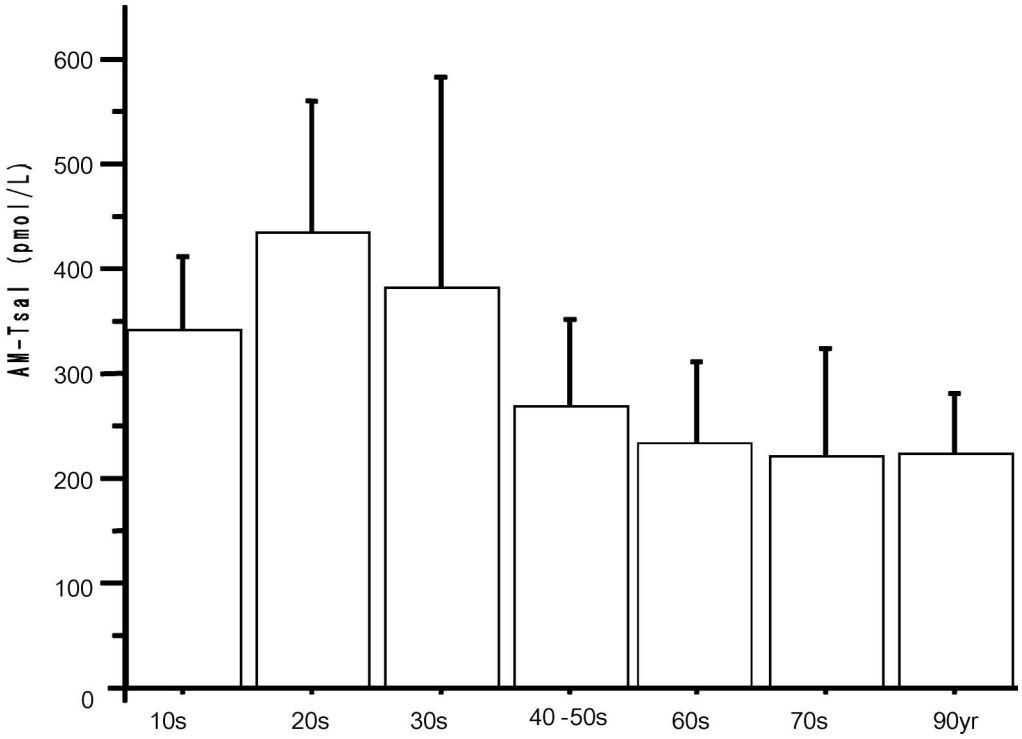

Figure 1. Morning salivary testosterone values (AM-Tsal) in Japanese males. Averages by age group are shown with 95% error bars.

testosterone levels also showed wide fluctuations, a pattern that was consistent through the 70s.

Discussion

Longitudinal studies with large sample numbers offer richer data than cross sectional investigations of endocrinological aging patterns within a population. Yet, cross sectional studies such as the present investigation, can still provide useful information regarding age related variation patterns. In addition, salivary steroid assessments allow for a painless and noninvasive methodology that is especially conducive to studies of older individuals. Salivary assessments also provide a reflection of the unbound bioactive fraction of steroids and are highly correlated with serum measurements [37–39].

As in western populations, Japanese males in this study group show a significant increase in salivary testosterone from the late teens to 20s with a distinct peak that is followed by significant decrease beginning at age 30. This pattern is different from those of the Ache of Paraguay, Nepalese, Central African, and Kenyan pastoral males that do not show a distinct peak during their 20s as is common among western populations possibly due to energetic constraints during fetal and adolescent development [7–12]. The Japanese pattern between the teens and 30s can be considered to be one that reflects a population that is probably not energetically limited.

The aging pattern of older (>40s) Japanese males also demonstrates a distinct feature. It has been a common notion that testosterone declines after the fifth decade even in healthy populations [3], although a few studies show no significant age-related decrease in serum total testosterone [14,15,40]. Western populations such as men from Boston, USA, exhibit a constant decline of average salivary testosterone values from their 20s through 70s [7]. Within the Japanese males in this study, there is no continuous decline with age after age 40 through 90s. Moreover, the relatively high testosterone values of 90 year olds are quite remarkable. The 90-year-old males in our study were all ambulatory and were able to attend the community centre study with little or no assistance, suggesting that overall health robusticity has a likely association with testosterone measured in saliva.

Jinrui et al. [16] reported that salivary testosterone among Japanese males decreases significantly after the age of 50. Judging from their figures, the decline was especially evident between the 30s and older groups, but was not marked among the 50, 60 and 70s age cohorts. Recent studies of healthy Japanese [15] and Chinese [14] males showed that calculated serum free testosterone but not serum total testosterone were significantly different between young (20–30s) and older (40–70s) individuals. These results, as well as those of the current study, which shows no significant age-related decline in salivary testosterone levels after middle age, perhaps reveal the possible influence of greater sex hormone binding globulin (SHBG) production or binding at older ages. Based on the comparison between nomadic and settled Turkana populations, Campbell et al. [12] suggested that the population variation in aging pattern of free serum and salivary testosterone may reflect energy status through the effect of SHBG. The differences between western countries and these

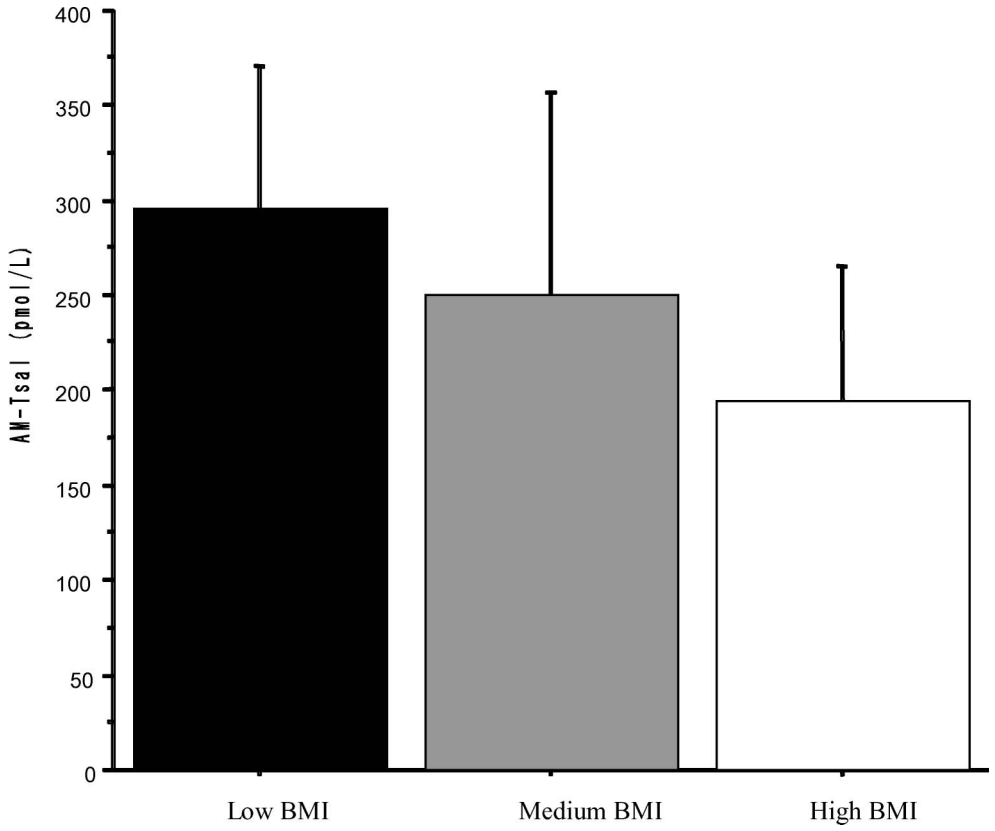

Figure 2. Body Mass Index (BMI) and morning salivary testosterone values in 40–70s. Averages by BMI category is shown with 95% error bars. Low BMI ($n = 17$) < 22.5; $22.5 <$ Medium BMI ($n = 18$) < 25.5; High BMI ($n = 18$) > 25.5. After log transformation, the T-sal of Low-BMI group is significantly different from that of High-BMI group ($p < 0.05$, t-test).

Table II. Intraindividual fluctuation in salivary testosterone levels by age-group.

Age (*n*)	T-intraindividual fluctuation Mean (pmol/L)	SD
15–19 (18)	305.0*	169.6
20s (16)	314.1*	171.7
30s (12)	295.8*	265.8
40s & 50s (18)	232.8	151.1
60s (22)	222.3	165.3
70s (13)	200.0	155.4

*: After log transformation, significantly different from 70s by t-test ($0.05 > p > 0.01$), n.s. Scheffe's test.

Asian populations, however, are not likely to be due to differences in energy availability and usage. The Japanese data of this study support the notion that the constant and significant decline in testosterone after the age of 50 commonly reported in the clinical literature, may not be universal. In addition to comparisons between young and old male groups, more analyses of age-related changes among middle aged and elderly males within industrialized populations may be fruitful.

The relationship between BMI and salivary testosterone values between 40–70s among Japanese males provides further support to previous studies that suggest an association between salivary testosterone and body composition [11,12,41]. It should also be noted that recent studies of serum total testosterone among US and Norwegian populations showed that waist circumference is a better predictor of serum T levels than BMI [24,25]. Variation in salivary testosterone values with age may not be simply viewed as an inevitable aging pattern per se [7,11,30,31].

Decreases in the range of intraindividual testosterone fluctuation as a typical aging pattern were not confirmed within our Japanese study group. Many Japanese males in their 60s and 70s show not only relatively high maximum values, but also maintain a broad range of intraindividual fluctuation, similar to those in their 40–50s. Diver et al. [42] found no significant changes in diurnal rhythm of serum total, free and bioavailable testosterone or of SHBG among normal males in the UK. Future studies might consider if testosterone fluctuation could be used as an indicator of a 'robust' endocrine system in elderly men.

The significance of androgens in older male cognitive function as well as physical maintenance such as bone density and muscle mass has been widely reported [20,27,43–48]. Yet, the potential merits of the clinical application of androgen hormone treatment are still in question [49,50]. This may be due to experimental designs in which

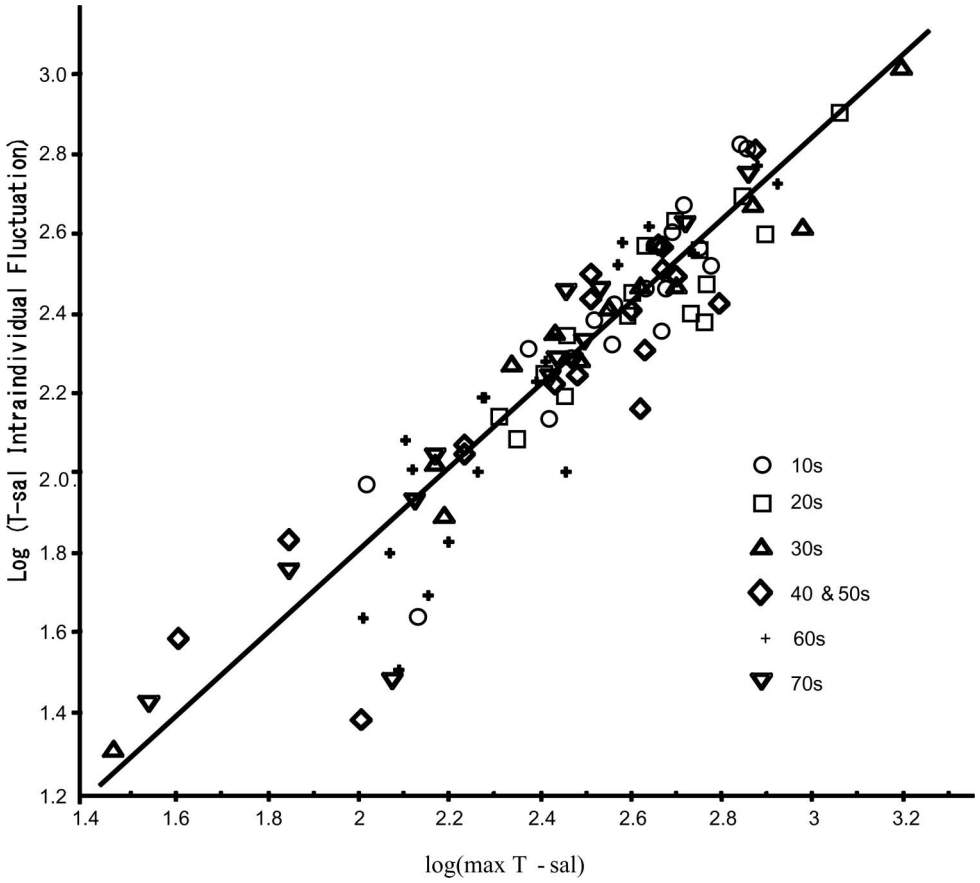

Figure 3. Intraindividual fluctuation and the maximum testosterone value (log value). $Y = -0.293 + 1.043 * X$; $R^2 = 0.862$, $p < 0.001$.

results are largely affected by different sources of variation, such as populations living under contrasting lifestyle and environmental circumstances. Also, we should not focus on absolute testosterone values that may not fully reveal the complexity of neuroendocrine system function [6,51,52].

Although the Japanese are considered to be an industrialized population in terms of energy availability and utilization, they demonstrate an aging pattern that is distinct from other groups. Maintaining relatively high and significantly fluctuating testosterone values seems to be associated with long, healthy, and active lives among Japanese males. How they attain this pattern should be further investigated by looking at the whole neuroendocrinological system as well as their genetic basis and social environment. In summation, the aging pattern of endocrinological function varies among individuals and between populations. Well designed research programmes on such variation would be of considerable importance for the proper application of hormone treatment therapy or the development of a hormonally based male contraceptive.

Acknowledgement

We thank all of the study participants and those who helped us with sample collection. For data analyses and stimulating discussions, we thank the members of Reproductive Ecology Laboratories within the Departments of Anthropology at Yale and Harvard University. The Japan Society for the promotion of Science and a grant from Smith Klein Beecham, Inc. to (PTE) funded this research.

References

1. Ferrini RL, Barrett-Connor E. Sex hormones and age: A cross-sectional study of testosterone and estradiol and their bioavailable fractions in community-dwelling men. Am J Epidemiol 1998;147:750–754.
2. Gray A, Feldman HA, McKinlay JB, Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: Results of the Massachusetts Male Aging Study. J Clin Endocrinol Metab 1991;73(5):1016–1025.
3. Harman SM, Miller EJ, Tobin JD, Person J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal study of Aging. J Clin Endocrinol Metab 2001;6:724–731.
4. Matsumoto AM. Andropause: Clinical implications of the decline in serum testosterone levels with aging in men. J Gerontology Series A Biol Sci Med Sci 2002;572:M76–M99.
5. Nahoul K, Roger M. Age-related decline of plasma bioavailable testosterone in adult men. J Steroid Biochem 1990;35: 293–299.
6. Sievert LL. Aging and reproductive senescence. In: Ellison PT, editor. Reproductive ecology and human evolution. Hawthorne, NY: Aldine de Gruyter; 2001. pp 267–292.
7. Ellison PT, Bribiescas RG, Bentley GR, et al. Population variation in age-related decline in male salivary testosterone. Hum Reproduction 2002;17:3251–3253.

8. Bribiescas RG. Testosterone levels among Aché hunter/gatherer men: A functional interpretation of population variation among adult males. Hum Nat 1996;72:163–188.
9. Bribiescas RG. Reproductive physiology of the human male in evolutionary and life history perspective. In: Ellison PT, editor. Reproductive ecology and human evolution. Hawthorne, NY: Aldine de Gruyter; 2001. pp 107–133.
10. Ellison PT, Panter-Brick C. Salivary testosterone levels among Tamang and Kami males of central Nepal. Hum Biol 1996;686:955–965.
11. Campbell B, O'Rourke MT, Lipson SL. Salivary testosterone and body composition among Ariaal males. Am J Hum Biol 2003;18(1):71–82.
12. Campbell B, Leslie P, Campbell K. Age-related changes in testosterone and SHBG among Turkana males. Am J Hum Biol 2006;18(1):71–82.
13. Kang YG, Bae CY, Kim S, Kim MJ, Lee YJ, Seo J, Kim YC. Age-related change in serum concentrations of testosterone in middle-aged Korean men. Aging Male 2003;6(1): 8–12.
14. Li JY, Li XY, Li M, Zhang GK, Ma FL, Liu ZM, Zhang NY, Meng P. Decline of serum levels of free testosterone in aging healthy Chinese men. Aging Male 2005;(3–4):203–206.
15. Sato Y, Tanda H, Kato S, Onishi S, Nakajima H, Nambu A, Nitta T, Korku M, Akagashi K, Hanazawa T, et al. Serum testosterone levels using the radioimmunoassay method in healthy Japanese male volunteers. Reproductive Medicine and Biology 2006;5(1):37–41.
16. Jinrui H, Itoh N, Nitta T, Kurohata T, Tsukamoto T, Kumamoto T, Umehara T. Changes in the salivary testosterone level in aged. Hinyokiyo 1994;40(9):807–811.
17. Ongphiphadhanakul B, Rajatanavin R, Chailurkit L, Piaseu N, Teerarungsikul K, Sirisriro R, Komindr S, Puavilai G. Serum testosterone and its relation to bone mineral density and body composition in normal males. Clin Cndocrinol (Oxf) 1995;43(6):727–733.
18. Spratt DI, Cox P, Orav J, Moloney J, Bigos T. Reproductive axis suppression in acute illness is related to disease severity. J Clin Endocrinol Metab 1993;76(6):1548–1554.
19. Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N, Chen X, Yarasheski KE, Magliano L, Dzekov J, et al. Testosterone dose-response relationships in healthy young men. Am J Physiol Endocrinol Metab 2001;281(6): E1172–E1181.
20. Bhasin S, Woodhouse L, Casaburi R, Singh AM, Mac RP, Lee M, Yarasheski KE, Sinha-Hikim I, Dzekov J, Magliano L, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 2005;90(2):678–688.
21. Snyder PJ, Peachey H, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ, Strom BL. Effect of testosterone on body composition and muscle strength in men over 65 year of age. J Clin Endocronol Metab 1999;84:2647–2653.
22. Dicker A, Ryden M, Naslund E, Muehlen IE, Wiren M, Lafontan M, Arner P. Effect of testosterone on lipolysis in human pre-adipocytes from different fat depots. Diabetologia 2004;47(3):420–428.
23. Tsai EC, Boyko EJ, Leonetti DL, Fujimoto WY. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. Int J Obes Relat Metab Disord 2000;24(4):485–491.
24. Derby CA, Zilber S, Brambilla D, Morales KH, McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. Clin Endocrinol 2006;65:125–131.
25. Svartberg J, von Mühlen D, Sundsfjord J, Jorde R. Waist circumference and testosterone levels in community dwelling men. The Tromsø study. Euro J Epidemiol 2004;19(7):657–663.
26. Vermeulen A, Goemaere S, Kaufman JM. Testosterone, body composition and aging. J Endocrinol Invest 1999;225(Suppl.): 110–116.
27. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999;84:3681–3685.
28. Bribiescas RG. Age-related differences in serum gonadotropin (FSH and LH), salivary testosterone, and 17-beta estradiol levels among Ache Amerindian males of Paraguay. Am J Phys Anthropol 2005;127:114–121.
29. Bribiescas RG. On the evolution, life history, and proximate mechanisms of human male reproductive senescence. Evol Anthropol 2006;15(4):132–141.
30. Feldman HA, Longcore C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts Male Aging study. J Clin Endocrinol Metab 2002;872: 589–598.
31. Nieschlag E, Lammers U, Freischem CW, Langer K, Wickings EJ. Reproductive function in young fathers and grandfathers. J Clin Endocrinol Metab 1982;55:676–681.
32. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983;566:1278–1281.
33. Japanese Ministry of Health, Labour and Welfare. Annual report on the Japanese life table 2004–2005.
34. Robine JM, Saito Y, Jagger C. The emergence of extremely old people: The case of Japan. Exp Gerontol 2003;38(7): 735–739.
35. Marugame T, Mizuno S. Comparison of prostate cancer mortality in five countries: France, Italy, Japan, UK and USA from the WHO mortality database (1960–2000). Jpn J Clin Oncol 2005;35(11):690–691.
36. Lipson SF, Ellison PT. Development of protocols for the application of salivary steroid analyses to field conditions. Am J Hum Biol 1989;1:249–255.
37. Navarro MA, Gomez JM, Villabona CM, Bonnin R. Salivary testosterone: A good measure to reflect free testosterone. Arch Intern Med 1987;147:1189.
38. Navarro MA, Juan L, Bonnin MR, Villabona C. Salivary testosterone: Relationship to total and free testosterone in serum. Clin Chem 1986;32:231–232.
39. Wang C, Plymate S, Nieschlag E, Paulsen CA. Salivary testosterone in men: Further evidence of a direct correlation with free serum testosterone. J Clin Endocrinol Metab 1981;53: 1021–1024.
40. Khosla S, Melron J III, Atkinson EJ, O'Fallon WM. Relationship of serum sex steroid levels to longitudinal changes in bone density in young versus elderly men. J Clin Endocrinol Metab 2001;86:3555–3561.
41. Bentley GR, Harrigan AM, Campbell BC, Ellison PT. Seasonal effects on salivary testosterone levels among Lese males of the Ituri forest, Zaire. Am J Hum Bio 1995;5: 711–717.
42. Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clin Endocrinol (Oxf) 2003;58(6): 710–717.
43. Kenny AM, Prestwood KM, Marcello KM, Raiz LG. Determinants of bone density in healthy older men with low testosterone levels. J Gerontol A Bio Sci Med Sci 2000;55: M492–M497.
44. Moffat S, Zonderman AB, Metterm EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;8711:5001–5007.
45. Van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationship with muscle strength, bone density, and body composition in elderly men. J Clin Endocrinol Metab 2000;85: 3276–3282.

46. Wolf OT, Kirchbaum C. Endogeneous estradiol and testosterone levels are associated with cognitive performance in older Women and Men. Horm Behav 2002;41: 259–266.
47. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, Raskind MA, Brodkin K, Bremner W, Petrova A, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurol 2001;571:80–88.
48. Francis RM. The effects of testosterone on osteoprosis in men. Clin Endocrinol 1999;50:411–414.
49. Kaufmann JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical therapeutic implications. Endocrine Review 2005;26(6):833–876.
50. Yaffe K, Lui L-Y, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriat Soc 2002;50: 707–712.
51. Mitchell R, Hollis S, Rothwell C, Robertson WR. Age-related changes in the pituitary-testicular axis in normal men: Lower serum testosterone results from decreased bioactive LH drive. Clin Endocrinol 1995;42: 501–507.
52. Muehlenben MP, Bribiescas RG. Testosterone-mediated immune functions and male life histories. Am J Hum Biol 2005;17:525–558.