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Testosterone is associated with age-related changes in bone health status, muscle strength and body composition in men

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***Objective*: Variations in testosterone levels are associated with several outcomes of aging. The present study aimed to examine the relationship between age-related decline of testosterone levels and changes in bone health status, handgrip strength, body fat percentage and fat-free mass. *Materials and methods*: A total of 335 Malaysian Chinese and Malay men aged 40 years and above were recruited for this study. Their body compositions, calcaneal speed of sound and handgrip strength were measured and their blood was collected. Linear regression analysis was done to examine the relationship among age, testosterone levels and outcomes of aging. *Results*: The results indicated significant changes in all testosterone measurements, sex hormone binding globulin level, calcaneal speed of sound, handgrip strength, body fat percentage and fat-free mass with age ($p < 0.05$). Age-dependent decline in bioavailable and free testosterone levels were significantly associated with reduction in calcaneal speed of sound, fat-free mass and handgrip strength ($p < 0.05$). Age-dependent decline in the total testosterone level was significantly associated with an increase in body fat percentage among the elderly men ($p < 0.05$). *Conclusion*: Testosterone levels are associated with changes in outcome of aging such as bone health status, muscle strength and body composition, and the relationships are age-dependent.**

Keywords: Testosterone, calcaneal speed of sound, body composition, handgrip strength, men

Introduction

Aging is accompanied by physiological changes, such as reduction in bone health status[1,2], muscle strength [2] and fat free mass [3]. These changes are related to frailty, functionality and survival of aging men. Previous studies indicated that men who suffer from osteoporotic fractures have higher mortality and morbidity compared to their female counterpart [4]. Bone density at hip is associated with all-cause and cardiovascular mortality in elderly men [5]. Grip strength is also a useful predictor of mortality, morbidity and functionality in the elderly population [6]. Besides, it is proposed as the single marker of frailty in men [7]. Mortality in elderly men is also associated with variation in body composition indicators such as fat and fat-free mass [8].

It is now recognized that there is an age-associated decrease in androgen level in men. This is coupled with the rise of serum sex hormone binding globulin (SHBG) in men, which further reduces the availability of testosterone to its target tissues [9]. Since the decline is slow and progressive, this phenomenon is termed 'late-onset hypogonadism' [10] or 'testosterone deficiency syndrome' [11]. The decline in the bioavailability and the level of testosterone are proposed to be the reason of involutional osteoporosis [12], decrease in muscle strength [2] and alteration in body composition [2] in aging men.

Among the three measurements of testosterone (total, free and bioavailable testosterone), it is not known which will best predict the aforementioned outcomes of aging, or whether a single measurement will suffice to predict these outcomes in aging men. In the diagnosis of androgen deficiency, total testosterone measurement will be sufficient in most of the cases, but free and bioavailable testosterone should be taken into account when there is a substantial change in SHBG level [13]. Free testosterone refers to the testosterone fraction unbound by SHBG while bioavailable testosterone refers the

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sum of the unbound fraction and the fraction bound loosely by albumin, which is readily available to the target tissues [14]. Besides, there are few available literatures on the relationship between testosterone and these outcomes of aging in a mixed population, whereby ethnicity may be a potential confounder that should be adjusted.

The present study aimed to examine the relationship between age-related decline of testosterone levels and changes in bone health status, handgrip strength, body fat percentage and fat-free mass. The strength of the three testosterone measurements, which are total, free and bioavailable testosterone, in predicting these outcomes of aging was compared. We hope these findings will generate a unified model using testosterone that would explain the changes in physiological functions, leading to frailty in aging men due to testosterone deficiency syndrome and suggest possible areas for intervention in preventing the progression of frailty, and in improving the quality of life among elderly men.

Materials and methods

Study design

This cross-sectional study was conducted as part of the Partial Endocrine Deficiency in Malaysian Men study and the sampling technique adopted was purposive sampling. Invitation with specific inclusion and exclusion criteria was advertised in major newspapers, radio broadcasts, flyers, and public announcements via community centers and religious places. The recruitment was conducted within the period of September 2009 and September 2011. The study protocol was reviewed and approved by the Ethics Committee of Universiti Kebangsaan Malaysia Medical Centre (UKMMC).

Study population

A total of 595 Malaysian men of Malay and Chinese ethnicity, aged 40 years and above and residing in the Klang Valley, which is situated in the central region of Peninsular Malaysia (Kuala Lumpur, Gombak, Petaling Jaya, Shah Alam and Klang), visited our screening center. Three hundred and forty four subjects consented and came for the blood collection. All subjects were screened using a detailed demographic questionnaire. Their medical conditions were based on history, basic physical examination performed by qualified physicians and previous medical records. Subjects taking medications known to affect testosterone level, such as corticosteroids and testosterone replacement were excluded from the study. Subjects having major systemic diseases that are pertinent to a change in testosterone levels, such as sexual dysfunction, cancer, osteoporosis/osteoporotic fracture and those who had undergone major surgery six months prior to the screening were excluded as well. All subjects were briefed in detail on information regarding to the study and written informed consent was obtained.

Body anthropometry measurement

Height of the subjects without shoes was estimated using Seca-213 portable stadiometer(SECA, Hamburg, Germany) and was recorded to the nearest 0.1 cm. The weight of the subjects with light clothing but without shoes was determined and was recorded to the nearest 0.1 kg. The weight, fat free mass, fat mass, and body fat percentage of the subjects were estimated using BC-418 Segmental Body Composition Analyzer (TANITA Corp., Tokyo, Japan), based on the principle of bioelectrical impedance. Briefly, the degree of difficulty (resistance) in which electrical current passes through the body (fat does not allow electricity to pass while water in tissues does) is used to infer the variables measured. The body composition analyzer uses a constant current source (50 kHz, 500 μA), which is supplied via the electrodes positioned on the tips of the toes of both feet and fingertips of both hands. The voltage is measured on the heel of both feet and thenar side of both hands.

Hand grip strength measurement

The muscle strength of the subjects was determined by hand grip strength, measured using a digital handgrip dynamometer (TKK 5401 Grip; Smedley, Takei, Tokyo, Japan). During the test the subjects stood with feet shoulder-width apart and their shoulder adducted and neutrally rotated. Their forearm and wrist were in neutral position and elbow extended fully. Subjects were required to keep the dynamometer away from any part of the body. Grip strength was measured for each hand and the average value was obtained from the reading of both hands.

Calcaneal speed of sound measurement

The bone health status of subjects was evaluated by the speed of sound traveling through the calcaneusof subjects, using the gel-coupled CM-200 sonometer (Furuno, Noshinimiya City, Japan). The speed of sound waves transmitting from a transducer to another through the right calcaneus would be analyzed and displayed by the computer. Three readings were obtained per subjects and the average value was used for analysis. All measurements were performed by a trained technician, and calibration was conducted prior to each screening session. Quality control was conducted using a phantom. In general, a higher calcaneal speed of sound value indicated better bone health status.

Hormonal assay

All subjects were required to fast for at least eight hours prior to the screening. During the fasting period, subjects were not allowed to consume any food or beverages except for plain water. Blood collection was conducted between 08:30 and 10:30. The blood was collected in plain tubes and the serum was extracted. Part of the serum was sent immediately for total testosterone and albumin assays. The remaining serum was stored at –70°C for 1–6 months for sex hormone binding globulin (SHBG) assay. Total testosterone level was determined using ADVIA Centaur (Siemens Healthcare Diagnostics, Illinois, USA) based on competitive immunoassay with direct chemiluminescent technology (inter-assay CV = 5.00–6.32%, minimum detection limit = 0.347 nmol/l). The albumin level was determined using ADVIA 2400 (Siemens Healthcare Diagnostics, Illinois, USA) based on the bromcresol green method (inter-assay CV = 1.75%). The SHBG

level was measured using solid phase enzyme-linked immunosorbent assay (ELISA) kits (IBL International, Hamburg, Germany) (inter-assay CV = 3.1–8.0%). The test procedures and principles were conducted per manufacturers' instructions. The free and bioavailable testosterone levels were calculated using formulae previously introduced by Södergård et al. (1982) [15].

Data analysis

Normality of the data were determined using the Shapiro–Wilk test. Body fat percentage was used for analysis rather than fat mass because the distribution of body fat percentage was normal but for fat mass was skewed. The differences in all variables between Chinese and Malay men were examined using independent t-tests. Linear regression was used to determine the relationship between age or bioavailable testosterone and studied variables (bioavailable testosterone, calcaneal speed of sound, fat free mass, body fat percentage and hand grip). Unstandardized regression coefficient (*B*) indicated the change of the studied variable when the predictor (age or bioavailable testosterone) changed by 1 unit. Standardized regression coefficient (β) measured the changes when the predictor changed by one standard deviation. All linear regression was adjusted for BMI and ethnicity, or ethnicity alone. The significance was set at $p < 0.05$. The data were analyzed using the Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago, USA) software.

Results

A total of 344 subjects with complete hormonal profiles were eligible for this study. Nine subjects were excluded due to incomplete anthropometric measurements. Data from 335 subjects, which consisted of 223 Chinese and 112 Malay men, were used for analysis. The overall mean age of the subjects was 54.24 years (SD = 9.66 years), with a range of 40–83 years.

Independent t-test revealed that there were significant differences between Chinese and Malay men in most of the variables studied ($p < 0.05$) except testosterone, sex hormone binding globulin levels and calcaneal speed of sound ($p > 0.05$). The Chinese men were significantly younger, taller and had lesser weight, BMI, body fat percentage and fat free mass, but higher handgrip measurement compared to their Malay counterpart ($p < 0.05$). The testosterone levels and calcaneal SOS value did not differ significantly between the Malays and the Chinese ($p > 0.05$). Based on these findings, ethnicity was controlled for the subsequent linear regression analysis (Table I).

Linear regression indicated that there were significant age-related decreases in calcaneal speed of sound, fat free mass and handgrip ($p < 0.05$). Overall decrement of –0.546 m/s calcaneal speed of sound, –0.166 kg fat free mass and –0.287 kg in handgrip per year was observed in our subjects. There was also a significant age-related decline in all testosterone measurements ($p < 0.05$), in which a –0.123 nmol/l reduction in total testosterone, a –0.144 nmol/l reduction in bioavailable testosterone and a –0.005 nmol/l reduction in free testosterone per year were observed. A minimal but significant increase in body fat percentage (0.051% per year) was found in men when their age increased ($p < 0.05$) (Table II).

Further analysis revealed that total, bioavailable and free testosterone predicted the outcomes of aging at varying degrees. The relationships between total testosterone and calcaneal speed of sound (β = 0.115), fat free mass (β = 0.057) and handgrip (β = 0.112) were positive but not significant ($p > 0.05$), but its relationship with body fat percentage (β = –0.068) was negative and significant ($p < 0.05$). The relationship between bioavailable testosterone and calcaneal speed of sound (β = 0.132), fat free mass (β = 0.119) and handgrip (β = 0.142) were positive and significant ($p < 0.05$) but its relationship with body fat percentage (β = –0.038) was negative but not significant ($p > 0.05$). The relationships between free testosterone and calcaneal speed of sound (β = 0.145), fat free mass (β = 0.122) and handgrip (β = 0.219) were positive and significant ($p < 0.05$) but its relationship with body

Table I. General characteristics of the study population.

Variable	Chinese (*n* = 223)	Malay (*n* = 112)	Overall (*n* = 335)	Sig.
Age	53.17 (8.97)	56.34 (10.64)	54.23 (9.66)	s
Height (cm)	167.00 (6.33)	164.63 (6.00)	166.21 (6.31)	s
Weight (kg)	68.25 (11.05)	74.33 (15.20)	70.28 (12.89)	s
BMI (kg/m2)	24.42 (3.48)	27.37 (5.11)	25.43 (4.32)	s
Body fat (%)	22.83 (5.45)	25.46 (7.12)	23.71 (6.19)	s
FFM (kg)	52.27 (6.23)	54.64 (7.26)	53.06 (6.67)	s
SOS (m/s)*	1511.7 (27.62)	1518.36 (24.73)	1513.94 (26.84)	ns
Handgrip (kg)	34.37 (6.06)	31.84 (7.28)	33.53 (6.60)	s
Total T (nmol/l)	18.97 (7.71)	18.66 (6.27)	18.76 (6.78)	ns
Bio T (nmol/l)	10.11 (3.31)	10.38 (3.46)	10.20 (3.36)	ns
Free T (nmol/l)	0.36 (0.12)	0.38 (0.13)	0.37 (0.12)	ns
SHBG (nmol/l)	49.85 (26.11)	46.84 (25.63)	48.8 (25.95)	ns

BMI, body mass index; FFM, fat-free mass; T, testosterone; SOS, calcaneal speed of sound; SHBG, sex hormone binding globulin.
The values of all variables were expressed in mean (standard deviation). 'Sig.' indicates significance of the independent t-test between Chinese and Malay subjects. Letter '*s*' indicates a significance difference ($p < 0.05$) in the variable tested while '*ns*' indicates an insignificant difference ($p > 0.05$).
*Insignificant after adjustment for height and body weight.

Table II. Linear regression results when outcome of aging is regressed against age.

	Age		
	Regression coefficient		
Variable	Unstandardized	standardized	*p*
SOS (m/s)	–0.546	–0.197	<0.001
FFM (kg)	–0.166	–0.241	<0.001
Body Fat (%)	0.051	0.079	<0.05
Handgrip (kg)	–0.287	–0.42	<0.001
Total T (nmol/l)	–0.123	–0.175	<0.001
Bio T (nmol/l)	–0.144	–0.414	<0.001
Free T (nmol/l)	–0.005	–0.378	<0.001
SHBG (nmol/l)	0.622	0.231	<0.001

FFM, fat-free mass; T, testosterone; SOS, calcaneal speed of sound; SHBG, sex hormone binding globulin.
Unstandardized regression coefficient (*B*) indicates the change of the studied variable when the predictor (age) changes by 1 unit. Standardized regression coefficient (β) measures the changes when the predictor changes by one standard deviation. The predictor in this table is age.

Table III. Linear regression results when outcome of aging is regressed against testosterone levels.

	Total T			Bio T			Free T		
	Regression coefficient			Regression coefficient			Regression coefficient		
Variable	unstandardized	standardized	*p*	unstandardized	standardized	*p*	unstandardized	standardized	*p*
SOS (m/s)	0.454	0.115	0.062	1.075	0.132	0.02	32.236	0.145	0.011
FFM (kg)	0.056	0.057	0.187	0.229	0.119	0.003	6.722	0.122	0.002
Body fat (%)	–0.062	–0.068	0.017	–0.067	–0.038	0.153	–2.444	–0.048	0.071
Handgrip (kg)	0.109	0.112	0.065	0.271	0.142	0.008	11.937	0.219	<0.001

FFM, fat-free mass; T, testosterone; SOS, calcaneal speed of sound; SHBG, sex hormone binding globulin.
Unstandardized regression coefficient (B) indicates the change of the studied variable when the predictor (testosterone levels) changes by 1 unit. Standardized regression coefficient (β) measures the changes when the predictor changes by one standard deviation. The predictors in this table are the testosterone measurement.

fat percentage (β = –0.048) was negative but not significant ($p > 0.05$) (Table III).

When adjustment for age was done, the previous significant relationships between testosterone and calcaneal speed of sound, fat free mass and handgrip reverted to insignificant ($p > 0.05$). This implied that the relationship of bioavailable testosterone and calcaneal speed of sound, fat free mass and handgrip was dependent on age.

Discussion

The studied population was a mixed population of middle-aged and elderly Chinese and Malay men. There were significant differences in the body anthropometry between the two ethnic groups but it was unlikely that the differences were contributed by testosterone because no significant differences in testosterone levels were found between the two groups. Besides, the difference in body anthropometry between Malay and Chinese men in Malaysia was also found by other researchers [16,17], hence it was not an isolated finding for this study. For the linear regression analysis, the two groups were combined and analyzed together, but with adjustments for BMI and ethnicity. Total testosterone in the study population declined with increasing age, indicating testosterone deficiency syndrome did occur. There was also a rise in SHBG levels as the age of the subjects increased, which further depleted the availability of the testosterone in their body. The combined effects of these two phenomena were illustrated in the bioavailable and free testosterone levels, which declined as the age of the subjects increased. The standardized regression coefficient of the relationship between age and bioavailable testosterone was the highest, followed by free testosterone and lastly total testosterone, indicating the decline in bioavailable testosterone is the most prominent among all the testosterone measurements.

There was a decline in bone health status of the subjects in terms of calcaneal speed of sound with increasing age and it was best predicted by free testosterone and bioavailable testosterone, but not by total testosterone. This finding was confirmed by previous studies using calcaneal speed of sound as an indicator of bone health status. A study by Vanderschueren et al. (2010) showed that calcaneal speed of sound was significantly associated with free and bioavailable testosterone but not total testosterone in a group of middle-aged and elderly European men [18]. Calcaneal speed of sound was the most sensitive quantitative ultrasound index that responded to variation in bioavailable testosterone [19]. However, the significant relationship between bone health status and testosterone levels was lost after age-adjustment. This observation was similar to the findings of Araujo et al. (2008), in which testosterone levels were not correlated with bone mineral density at various sites after age-adjustment [20]. These findings indicate that the relationship between testosterone and bone health status of subject is possibly age-dependent. A recent systematic review by Moayyeri et al. (2012) indicated that calcaneal quantitative ultrasound measurement predicted different fracture outcomes in elderly men and women [21]. Osteoporotic fracture is a major cause of mortality and morbidity for elderly men [22]. Thus, age-dependent deterioration of bone health status in men caused by the decline in testosterone levels could have an impact on morbidity and mortality in the later stages of their life.

A concurrent decline in fat free mass with decreasing free and bioavailable testosterone was also observed in this study, and their relationship was significant. Fat-free mass was not significantly associated with total testosterone in the subjects. It was the reverse for total testosterone measurement, in which body fat percentage was associated significantly with total testosterone, but not with free and bioavailable testosterone. This may imply that the relationships between fat-free mass and body fat percentage with testosterone measurements were independent of each other. Early studies in hypogonadal males revealed that testosterone replacement could increase their fat-free mass [23]. Testosterone replacement also increased fat-free mass and decreased fat mass in elderly men [24]. A study by Bigaard et al. (2004) showed that fat mass and fat-free mass were shown to be predictive of mortality at all causes [25]. A 22-year Swedish prospective cohort study also confirmed that percentage of fat mass and fat-free mass is associated with mortality risk [8]. Besides, body fat is also predictive of disability in elderly men [26]. Therefore, age-dependent changes in elderly men caused by testosterone might probably responsible for the increased mortality and morbidity.

The decline of handgrip strength with age in men is a universal finding both locally [27,28] and in other population [29,30]. A systematic review by Bohannon (2008) indicated that handgrip strength could predict future outcomes in aging adults, which included mortality/survival, disability and functional dependency [6]. The present study indicated that handgrip strength as measured by the dynamometer decreased with increasing age and declining

free and bioavailable testosterone, but it had no significant relationship with total testosterone. This was similar to the finding of Chu et al. (2008), in which right grip strength of Chinese men was found to be associated with bioavailable testosterone but not with total testosterone [31]. The decrease in handgrip strength could be contributed by loss of muscle mass due to age-related decline in testosterone level [32], but estimation of muscle mass *per se* of subjects were not examined in the present study.

Previous study found that men with higher body mass index (BMI) had lower testosterone level. In a study by Wu et al., the influence of BMI on testosterone levels was greater than age in total testosterone, second to age in free testosterone and SHBG in a group of men aged 40–79 years [33]. BMI as indicator for obesity is indeed an important comorbidity for diseases and it is relatively easy to be measured. However, it does not discriminate between fat mass and muscle mass [34]. In this study, we discriminated between fat and fat-free mass in the measurement of body composition. We found that total testosterone level was associated with body fat, while free and bioavailable testosterone levels were associated with fat-free mass.

Overall, our results indicated that Chinese and Malay men in Malaysia experienced a significant decline in testosterone levels and elevated SHBG level with age, leading to a reduction of bioavailability of testosterone to the target tissues. These hormonal changes then manifested clinically through reduction of bone health status, muscle strength and changes in body anthropometry. These changes have been proven previously to be associated with morbidity and mortality in elderly men. With a growing elderly population in developed countries like Malaysia, this requires further actions to ensure the quality of life for the elderly. Hormone replacement or androgen receptor modulator therapy should be considered if the symptoms of age-dependent hypogonadism affect the daily life of the elderly. Previous studies had established that intervention with testosterone could improve muscle strength, body composition, quality of life and physical function in elderly men with low to borderline-low testosterone [35]. Long-term testosterone replacement also increased bone mass in aged men with hypogonadism[36].

Several limitations need to be considered in the interpretation of the results of this study. This study adopted a non-randomized purposive sampling method, which can introduce substantial selection bias into the study. This study involved the two largest ethnic groups in Malaysia (Malays and Chinese), but did not include Indians and other minorities, so the results are not suitable to be extrapolated to the whole Malaysian male population. The measurements used for bone health status (quantitative ultrasound), body composition (bioelectrical impendence) and muscle strength (handgrip dynamometer) are not the gold standard measurements, yet the devices are suitable and have been used in other epidemiological studies. The devices are chosen because they are portable, easy to use and can prevent attrition of subjects. Handgrip strength only measured the muscle strength of the upper extremities, but the muscle strength of the lower body is not examined in the present study. Since this is a cross-sectional study, subjects were not followed up to obtain information on their mortality and morbidity. Further prospective studies on this aspect could provide stronger evidence of the linkage among testosterone measurements, outcomes of aging and mortality/morbidity of subjects.

As a conclusion, changes in outcomes of aging closely related to morbidity, mortality and frailty in men such as calcaneal speed of sound, fat-free mass, body fat percentage and handgrip strength are significantly associated with variation of testosterone levels, but not independent of age. Bioavailable and free testosterone are the best testosterone measurements that predict calcaneal speed of sound, fat-free mass and handgrip strength but body fat percentage is best predicted by total testosterone.

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