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Prevalence of and risk factors for androgen deficiency in middle-aged men in Hong Kong

Samuel Yeung Shan Wong[a,*], Dicken C.C. Chan[b], Athena Hong[b], Jean Woo[a,c]

[a]*Department of Community and Family Medicine, School of Public Health, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, N.T., Hong Kong.*
[b]*Jockey Club Centre for Osteoporosis Care and Control, The Chinese University of Hong Kong, Hong Kong*
[c]*Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong*

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Abstract

The purpose of this investigation was to study the prevalence of and risk factors for androgen deficiency in middle-aged men in Hong Kong. A community-based, cross-sectional household survey was performed in Hong Kong on men aged 45 to 64 years. Demographics, lifestyle information (cigarette smoking, alcohol consumption, and physical activity), and symptoms previously defined for identifying those with androgen deficiency were measured by using standardized questionnaires. Blood samples were collected in the morning, and total, free, and bioavailable testosterone levels were assessed. Data on androgen deficiency were available for 252 men aged 45 to 64 years. Crude prevalence of androgen deficiency was 9.52%. Prevalence increased significantly with age. For risk factors, having a lower personal income and having a history of hypertension were independently associated with increased risk of having androgen deficiency (odds ratio, 3.72; confidence interval, 1.01-13.61; and odds ratio, 2.89; confidence interval, 1.06-7.91, respectively). The prevalence of androgen deficiency in Hong Kong Chinese is similar to that found in Caucasians by using a similar definition. From this age-specific prevalence cross-sectional data, it is estimated that there are approximately 68,775 Hong Kong Chinese men aged 45-64 years with androgen deficiency. Future studies with large sample size are needed to evaluate the risk factors for androgen deficiency in men.

1. Introduction

Middle age is a critical phase in a man's life, a time when men undergo physical, psychologic, and physiologic changes. In the past 10 to 15 years, these age-related changes in men have attracted both scientific and commercial interests. One of the key questions for researchers is whether the decline of testosterone levels is responsible for the physical, psychologic, and physiologic changes in aging men. To this end, testosterone replacements have been advocated as treatments that can reverse these changes, often without strong evidence for their effectiveness [1].

Although it is well known that total testosterone levels decline by 1% to 2% annually in men starting at the age of 40 years, the clinical significance of this decline is still unknown. Furthermore, although the term "andropause" or "partial androgen deficiency in the aging man" has been used to refer to the nonspecific symptoms experienced by aging men, how to best define andropause or androgen deficiency in man is still a matter of debate. A recent statement by the Second Annual Andropause Consensus group meeting [2], however, has attempted to operationally define "androgen deficiency" by taking both biochemical and clinical information into consideration. With this new and recent definition of androgen deficiency, the epidemiology of androgen deficiency in Caucasian men aged 40 to 69 years [3] was described for the first time. It was found that approximately 2.4 million 40- to 69-year-old American men were affected by androgen deficiency and the incidence rate of androgen deficiency was 12.3 per 1000 person-years with significant increase with age.

Findings from previous research [4,5] suggest that racial differences may exist in endogenous hormonal levels in pre- and postmenopausal women. Whether these differences exist in hormonal levels in men is unknown. Although Chinese constitute approximately one sixth of the world

* Corresponding author. Tel.: +852 2252 8774; fax: +852 2606 3500.
E-mail address: yeungshanwong@cuhk.edu.hk (S.Y.S. Wong).

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population, the epidemiology of androgen deficiency in Chinese men has never been described. The purpose of the present study is to describe the prevalence of androgen deficiency and to study potential risk factors associated with androgen deficiency in Chinese by using an operational definition that incorporates both signs/symptoms plus total and free testosterone.

2. Methods

2.1. Study population and sampling frame

Data from this study were obtained from a cross-sectional, population-based, household survey that was conducted from September 2003 to June 2004 in 2 territories (New Territories and Kowloon) of Hong Kong to evaluate the prevalence of and risk factors (lifestyle and medical) for major health problems in aging men. The present research was conducted to study the prevalence of and risk factors for androgen deficiency by using operational definitions used previously in a large cohort study in Caucasians [3].

The total population of Hong Kong is 6.7 million. Ninety-nine percent of families live in housing blocks, which are owned either by the families (private housing) or by the Hong Kong Special Administrative Region Government (public housing). There are no electorate registers or general practitioner registers in Hong Kong for population sampling. Cluster sampling is the most frequently used sampling method, wherein subjects are interviewed face-to-face in their homes [6].

Geographically, Hong Kong is made up of 3 parts, the New Territories, the Kowloon peninsula, and the Hong Kong island. Residents of the New Territories and Kowloon peninsula make up more than 80% of the population. In this survey, only housing blocks located in the New Territories and the Kowloon peninsula were sampled. A list of housing blocks in the New Territories and the Kowloon peninsula was obtained, and the housing blocks were stratified into private and public housing to ensure equal representation of both. Housing estates were then randomly chosen from each stratum to obtain an equal number of subjects in each stratum. Trained interviewers then visited all households identified in the respective sample. At each visit, eligibility for study enrollment was determined (men aged 45-64 years) and informed consent was obtained. This was followed by the administration of a standardized questionnaire, which took approximately 15 to 20 minutes to complete. Appointments were made to interview eligible subjects who were not available at the time of interview. Those who responded to the interviews were invited to the School of Public Health to have their blood samples taken for hormone measurements. The study was approved by the Joint Chinese University of Hong Kong and the New Territories East Cluster Clinical Research Ethics Committee.

2.2. Hormone measurements

Nonfasting blood samples were drawn in the early morning from 9 to 11 AM to control for diurnal variation in hormone levels in all subjects. Blood was kept in an ice-cooled container for transport and centrifuged within 6 hours. Serum was stored in 5-mL scintillation vials at −20°C, shipped to the laboratory within 1 week, and stored at −70°C until time of assay.

Serum free and bioavailable testosterone concentrations were obtained by using a calculator developed by the Hormonology Department, University Hospital of Ghent, Belgium [7]. The calculation was based on measured serum total testosterone, sex hormone–binding globulin (SHBG), and albumin concentrations, and was done according to the method by Sodergard et al [8]. Studies showed that there is excellent correlation between free testosterone calculated by this method and free testosterone concentration obtained by equilibrium dialysis [9].

Both serum total testosterone and SHBG concentrations were measured on an automated immunoassay analyzer, Immunlite 2000 (Diagnostic Products, Los Angeles, CA). Reagents were used according to the manufacturer's instructions and the analytical performance was within the manufacturer's specifications. The principle of measurement for serum total testosterone was based on a solid-phase, competitive chemiluminescent enzyme immunoassay. Total coefficients of variation (CVs) for serum total testosterone concentrations of 3.0 to 34.4 nmol/L ranged from 7.2% to 13.0%. The principle of measurement for SHBG was based on a solid-phase, two-site chemiluminescent immunometric assay. Total CVs for serum SHBG concentrations of 1.2 to 80 nmol/L ranged from 4.0% to 6.6%.

Serum albumin concentrations were measured on an automated analytical chemistry system, Modular Analytics (Roche Diagnostics, Mannheim, Germany), based on a colorimetric method using Bromcresol Green (BCG) dye binding. The reagent was used according to the manufacturer's instructions and the analytical performance was within the manufacturer's specifications. Total CVs for serum albumin concentrations were better than 3%.

The reference range for free testosterone concentration was obtained from a study [10] conducted in Chinese men aged 20 to 40 years, where the 10th percentile value of men was defined as cutoff of 0.3 mmol/L for androgen deficiency. This value was used in a recent study by Araujo et al [3] to evaluate the epidemiology of androgen deficiency.

2.3. Questionnaire

2.3.1. Demographic and medical information

A structured questionnaire was administered in person to each subject. All data were collected by self-report. The questionnaire included information on sociodemographic information that included age, employment status, education levels, and personal income. Medical history was collected by asking questions based on a list of common medical

problems followed by an open-ended question on the presence of doctor-diagnosed past medical disease. Use of medication was asked as open-ended questions. Lifestyle factors that include cigarette smoking, alcohol consumption, and physical activity were also collected, and methods were reported previously [11].

2.3.2. Androgen deficiency—operational definition

The operational definition of androgen deficiency in our study is based on a diagnostic algorithm used in a statement from the Second Annual Andropause Consensus Meeting [2] and a recent study by Araujo et al [3]. This approach combines both signs/symptoms of low testosterone levels and biochemical parameters (ie, total testosterone and free testosterone) in defining androgen deficiency.

The statement from the Second Annual Andropause Consensus Meeting identified 12 signs/symptoms associated with low testosterone levels. The study by Araujo et al [3] identified 8 of the 12 signs and symptoms. In our current study, only 7 of the 12 signs and symptoms were included, as only 7 of the 12 symptoms were included in the standardized questionnaires in this study. These included (1) loss of libido, (2) erectile dysfunction, (3) depression, (4) lethargy, (5) sleep disturbance, (6) irritability, and (7) depressed mood. Signs/symptoms not measured in our study included (8) inability to concentrate (9) osteoporosis, (10) loss of muscle strength, (11) regression of secondary sex characteristics, and (12) decreased interest in activities. Table 1 shows information on signs/symptoms available in our current study.

The presence of each individual sign/symptoms was defined as follows. Loss of libido, lethargy, sleep disturbance, irritability, and depressed mood were defined as yes or no responses (binary item). Erectile dysfunction was measured by the International Index of Erectile Function (IIEF), a multidimensional scale with excellent reliability, validity, and sensitivity. The abridged validated 5-item version (IIEF-5) [12] was used in this study. It was first translated into Chinese and then backtranslated into English by a team of experienced and bilingual "field workers" who had translated and participated in previous questionnaire surveys. Five items were selected from the IIEF-15 and were based on the ability to identify the presence or absence of ED and on adherence to the National Institutes of Health's definition of ED over the previous month. Erectile dysfunction was classified as normal (22-25), mild (12-21), moderate (8-11), and severe (5-7) based on the answers to the 5 questions. Any subject having mild, moderate, or severe symptom scores was considered as having a positive response for erectile dysfunction.

Depression was assessed by the validated Chinese shortened (10-item) version for Centre for Epidemiologic Studies Depression Scale (CES-D 10) [13], with scores ranging from 0 to 10. A cutoff of 4 or less was defined as being depressed. This screening tool has been well validated and highly recognized in worldwide community studies on depression [14-16]. The presence of any 3 or more of the 7 available signs/symptoms is used as the number of signs/symptoms that would trigger testosterone measurement in a clinical setting.

The version of the diagnostic algorithm outlined in the study by Araujo et al [3] was used in the current study in Fig. 1. Similar to the algorithm defined by Araujo et al and the statement from the Second Annual Andropause Consensus Meeting, men were classified, based on their androgen deficiency status, according to (1) presence of signs/symptoms, (2) total testosterone level, and (3) free testosterone level. Men were considered to have androgen deficiency if they met one of the following 2 conditions: (1) at least 3 signs/symptoms and total testosterone level less than 6.94 mmol/L or (2) at least 3 signs/symptoms and total testosterone level of 6.94 to 13.88 nmol/L and free testosterone level less than 0.3092 nmol/L.

2.4. Analysis and statistical methods

Estimates of the crude and age-specific prevalence of androgen deficiency were computed as the number of men with androgen deficiency divided by the total number of men who had the blood tests. Ninety-five percent confidence intervals (CIs) for prevalence were computed. For risk factors associated with androgen deficiency, crude odds ratios (ORs) and corresponding 95% CIs were computed for the associations between demographic (age, employment status, education levels, and personal incomes), lifestyle (cigarette smoking, alcohol consumption, and physical activity), and medical factors (self-report of doctor-diagnosed medical diseases that included hypertension, diabetes mellitus, and cardiovascular disease, and antihypertensive medications) and androgen deficiency. Any factors with significant association with androgen deficiency in the

Table 1
Signs/symptoms of androgen deficiency available

Sign/symptoms	Measure used as indicator of symptoms/signs	Response options
Loss of libido	"Do you have a decrease in libido (sex drive)?" (ADAM)	Binary
Erectile dysfunction	5-Item composite based on IIEF-5 [12] (past month)	Ordinal, 0-5
Depression	CES-D 10 [13] (past week)	Binary, using cutoff
Lethargy	"I could not get going" (CES-D) (past week)	Binary
Sleep disturbance	"Do you have sleep problems, such as difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, or sleeplessness? (ADAM)	Binary
Irritability	"Are you sad, grumpy or both?" (ADAM)	Binary
Depressed mood	"I felt depressed" (past week)	Binary

ADAM indicates androgen deficiency in aging men questionnaire by Morley et al [17].

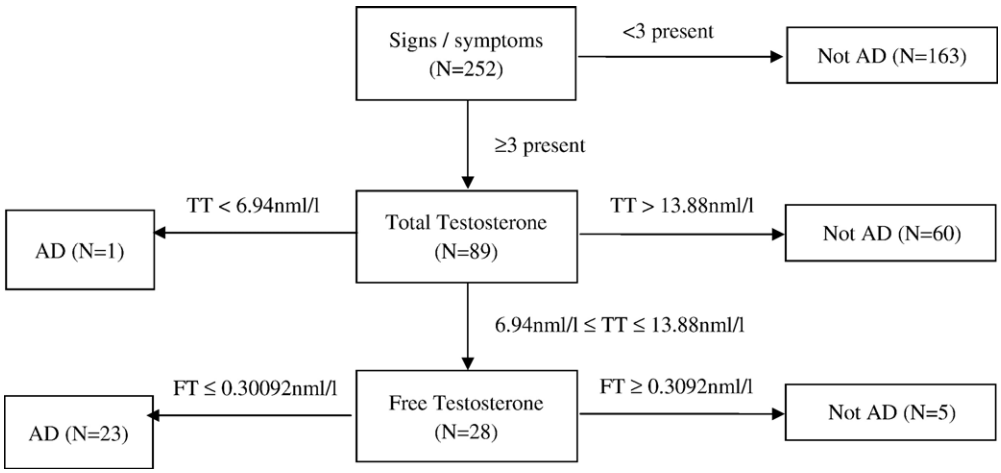

Fig. 1. Operational definition of androgen deficiency. TT indicates total testosterone; FT, free testosterone.

Prevalence of androgen deficiency = 9.52% (24/252)
Prevalence of androgen deficiency by age groups:
45-49 y: 8.20% (5/61), 95% CI (1.31-15.09)
50-54 y: 6.33% (5/79), 95% CI (0.96, 11.70)
55-59 y: 10% (7/70), 95% CI (2.97-17.03)
60-64 y: 16.67% (7/42), 95% CI (5.40-27.94)
Overall prevalence: 9.52% (24/252), 95% CI (5.90-13.14)

initial analyses were further examined in multiple logistic regression analysis. Data were analyzed by using the SAS statistical software (SAS Institute, Cary, NC). A 2-sided *P* value of .05 or less was considered as statistically significant.

3. Results

Three public housing estates (13 blocks) and 2 private housing estates (26 blocks) were visited by the trained interviewers. Of the 746 men in the appropriate age groups identified in these blocks, 538 men participated in this study with a response rate of 72.1%. The 538 men who agreed to an interview were also invited for an early morning total and free testosterone test. The conditional response rate for this group was 47%, with 252 men completing the full study.

The characteristics of the study population are shown in Table 2. Their mean age was 54.0 years. Ninety-three percent were married, 69.7% were currently employed, and 45.6% had primary or fewer years of education. A history of comorbid medical conditions included 6.5% men with diabetes and 19.2% with hypertension.

For the prevalence of androgen deficiency calculated by using the operational definition, the values obtained were 8.20% (95% CI, 1.31-15.09) for men aged 45 to 49 years, 6.33% (95% CI, 0.96-11.70) for men aged 50 to 54 years, 10% (95% CI, 5.40-27.94) for men aged 55 to 59 years, and 16.67% (95% CI, 5.90-13.14) for men aged 60 to 64 years. The overall prevalence was 9.52% (95% CI, 5.90-13.14).

For exploring risk factors for androgen deficiency, having an income of less than $9999 was marginally associated with increased odds of having androgen deficiency when compared with having an income of $20,000 or more (OR, 3.55; CI, 0.98-12.86; *P* = .054). Having a self-report history of hypertension was also marginally associated with increased odds of having androgen deficiency (OR, 2.50; CI, 0.99-6.26; *P* = 0.050) (Table 3). In multiple regression analysis, both

Table 2
Demographic variables (N = 252)

	No. (%)
Age (y)	
45-49	61 (24.41)
50-54	79 (31.35)
55-59	70 (27.78)
60-64	42 (16.67)
Mean	53.99
Marital status	
Married or living in a married-like relationship	235 (93.25)
Divorced/separated/widowed	8 (3.17)
Single, never married	9 (3.57)
Living status	
Live with others	247 (98.02)
Live alone	5 (1.98)
Educational achievement	
Graduated from college or university	60 (23.81)
Secondary school	77 (30.56)
Primary School or less	115 (45.63)
Job	
Full/part time	175 (69.72)
Retired	48 (19.12)
Unemployed	28 (11.16)
Income	
Less than $9999	102 (44.16)
$10,000-$19,999	59 (25.54)
$20,000 or above	70 (30.30)

Table 3
Bivariate associations between androgen deficiency and potential covariates, comparing those not androgen deficient and androgen deficient (N = 252)

	No. (%)	OR (95% CI)	*P*
Sociodemograpics			
Age			
45-49	61 (24.21)	1	
50-54	79 (31.35)	0.757 (0.209-2.742)	.6713
55-59	70 (27.78)	1.244 (0.374-4.143)	.7216
60-64	42 (16.67)	2.240 (0.659-7.609)	.1961
Educational achievement			
Graduated from college or university	60 (23.81)	1	
Secondary school	77 (30.56)	0.365 (0.087-1.524)	.1669
Primary school or less	115 (45.63)	1.350 (0.495-3.680)	.5576
Job			
Full/part time	175 (69.72)	1	
Retired	48 (19.12)	1.337 (0.456-3.918)	.5963
Unemployed	28 (11.16)	2.500 (0.823-7.591)	.1058
Income			
$20,000 or above	70 (30.30)	1	
$10,000-$19,999	59 (25.54)	1.624 (0.349-7.566)	.5369
Less than $9999	102 (44.16)	3.552 (0.981-12.863)	.0535
Lifestyle			
Cigarette smoking status			
Never smoker	140 (55.56)	1	
Former smoker	49 (19.44)	0.800 (0.250-2.557)	.7067
Current smoker of <20 cigarettes per day	33 (13.10)	1.241 (0.381-4.049)	.7200
Current smoker of ≥20 cigarettes per day	30 (11.90)	0.643 (0.138-2.990)	.5732
Alcohol consumption			
Had less than 12 drinks in the past 12 mo	144 (57.14)	1	
Current drinker of <7 alcoholic drinks per week	72 (28.57)	0.727 (0.272-1.946)	.5259
Current drinker of ≥7 alcoholic drinks per week	36 (14.29)	0.471 (0.103-2.147)	.3304
Physical activity			
Walking or Standing indoors <1 hour/d	43 (17.20)	0.702 (0.199-2.474)	.5816
Walk on level ground outdoor <3 hours/wk	40 (16.00)	0.770 (0.218-2.725)	.6857
Do outdoor exercise <3 hours/wk	186 (74.40)	0.614 (0.247-1.525)	.2933
Walk uphill <3 hours/wk	214 (85.60)	0.569 (0.197-1.645)	.2981
Walk with a load of 5 kg or more <3 hours/wk	217 (86.80)	1.015 (0.284-3.625)	.9815
Medical history			
Cardiovascular disease[a]	5 (1.98)	–	–
Diabetes mellitus	18 (7.14)	1.205 (0.260-5.586)	.8120
Hypertension	46 (18.25)	2.500 (0.999-6.257)	.0503
Antihypertensive medication	44 (17.46)	2.126 (0.824-5.485)	.1190

[a] No androgen deficient subject has cardiovascular disease.

factors continued to be independently associated with androgen deficiency in these men (income less than $9999 with OR, 3.72; CI, 1.01-13.61; hypertension with OR, 2.90; CI, 1.06-7.91) (Table 4). The prevalence of androgen deficiency also increased with advancing age, although it did not reach statistical significance. When age-specific prevalence of this study is applied to the Hong Kong Census Statistics data of men aged 45 to 64 years, we estimate that there are approximately 68,775 cases of androgen deficiency in this age group.

Table 4
Multivariate logistic regression model, comparing those not androgen deficient and androgen deficient

Characteristic	OR (95% CI)
Income	
$20,000 or above	1
$10,000-$19,999	1.565 (0.332-7.377)
Less than $9999	3.715 (1.014-13.612)*
Hypertension	2.898 (1.062-7.910)*

* $P < .05$.

4. Conclusions

To our knowledge, this is the first community-based study in middle-aged Chinese men that studied the prevalence of and risk factors for androgen deficiency by using a definition that includes both biochemical and clinical information. When our results were compared with the findings from the Massachusetts Male Aging Study [3], the prevalence was similar to those of the findings from the follow-up cohort of that study (7.1%-11.5% in the Caucasian study). Further comparison is difficult to make, however, because of the much smaller sample size in our study and the large variability of findings in the age-specific prevalence in our study.

The variability between the baseline and follow-up prevalence of androgen deficiency observed in the Araujo et al [3] study and the variability observed in prevalence in our study reflected the difficulty of defining androgen deficiency despite much effort by expert endocrinologists and researchers. Indeed, the use of any 3 symptoms and signs out of the 12 symptoms suggested by the Andropause Consensus Meeting to define androgen deficiency is somewhat arbitrary. What, and how many, signs and symptoms should be used together with testosterone levels to define androgen deficiency remains to be clarified by more epidemiologic and clinical research. Moreover, these signs and symptoms are often nonspecific. Although Morley et al [17] and Heinemann et al [18] have both constructed screening instruments for defining andropause in men, the nonspecificity of these symptoms and the lack of clear definition of andropause are still among the biggest problems for both researchers and clinicians. To evaluate if differences exist in the prevalence of androgen deficiency when using these 2 different definitions, it may be useful in future studies to use these screening instruments and the signs and symptoms described in the consensus together with testosterone levels to describe the prevalence of androgen deficiency.

In this study, few risk factors for androgen deficiency were identified. This could largely be due to the small sample size in our study, which has limited the power to detect any significant results. Although the sample size is small, however, low socioeconomic status seems to increase the risk of having androgen deficiency in men. As low socioeconomic status has been shown to affect a number of important health outcomes including quality of life [19], the results of this association further confirm the importance of social status in important health outcomes. However, the reason for hypertension as a risk factor for androgen deficiency is not known. No previous studies have been conducted that suggested hypertension as being a risk factor for symptoms associated with androgen deficiency. Consequently, with our small sample size and the lack of a convincing scientific explanation, this can be a spurious result.

In summary, the prevalence of androgen deficiency in this cross-sectional study is similar to findings from previous studies conducted in Caucasians that used a similar operational definition. The limitations in our current study included the small sample size, the lack of statistical power to identify risk factors, and the use of signs and symptoms that have not been formally validated. The strength in our study lies in its random, population-based design with the sample of men recruited from a well-defined geographic area. Furthermore, an operational definition of androgen deficiency based on the consensus meeting among experts in endocrinology and a previous large study was used, which allowed comparison of data. This operation is also more useful for clinical practice, as it uses both biochemical and clinical information to define androgen deficiency, which is closer to what clinicians encounter in their clinical settings. Moreover, the questionnaires were standardized and all interviewers received formal training before administration of these questionnaires with good quality assurance.

We provided the first population-based cross-sectional study on the prevalence of androgen deficiency by using an operationally defined syndrome of androgen deficiency. Future large studies will be needed to study risk factors associated with androgen deficiency in men.

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