Andropause in Indian Men
A Preliminary Cross-Sectional Study

Apul Goel, Rahul Janak Sinha, Divakar Dalela, Satyanarain Sankhwar, Vishwajeet Singh

Introduction: The purpose of this study was to determine the frequency of androgen decline in the aging male (ADAM) in a group of Indian men working in the health sector.

Materials and Methods: A free medical health checkup camp was organized for the male workers aged between 40 and 60 years employed in surgical departments of our hospital. Of 180 listed male workers, 170 attended this camp and 157 eligible men participated in the study. After clinical history and systemic inquiry, the participants were requested to complete the Saint Louis University's ADAM questionnaire, and their serum levels of free and total testosterone were measured.

Results: Symptomatic andropause was found in 106 men (67.5%) on the basis of their responses to the questionnaire, of whom 41 (38.7%) had low serum free testosterone levels and 32 (30.2%) had low serum levels of total testosterone. Fifty-one men were asymptomatic according to the questionnaire and in this group, 11 (21.6%) had low serum free testosterone levels and 6 (11.8%) of these had low total testosterone levels. The frequency of andropause was 33.1% on the basis of low serum free testosterone levels and it was 26.1% when both symptoms and low serum free testosterone levels were taken into account.

Conclusion: In our study, the high frequency of symptoms related to ADAM was unusual. This might be due to the nature of the questionnaire itself. Serum free testosterone measurement may be a better single test for diagnosis of hypogonadism than serum total testosterone measurement.

Keywords: andropause, aging, epidemiology, India

Urol J. 2009;6:40-6.
www.uj.unrc.ir

INTRODUCTION

Andropause or androgen decline in the aging male (ADAM) is a syndrome characterized by multiple clinical manifestations including erectile dysfunction, decreased libido, osteoporosis, generalized weakness, etc. Its occurrence is poorly documented and dichotomy exists regarding a true and accurate definition. Clinical diagnosis is problematic, since either serum testosterone levels or symptoms cannot accurately predict this condition. For diagnostic purpose, clinical judgment along with symptoms and a low testosterone level is considered important. This scenario is not always achievable and in such cases, a therapeutic trial is acceptable on the basis of symptoms alone.[1] Most of the literature on this subject is from Europe or North America.[2] We report a preliminary study documenting the frequency of ADAM in men aged between 40 and 60 years living in a city in India.

Department of Urology, Chhatrapati Shahuji Maharaj Medical University, Lucknow, Uttar Pradesh, India

Corresponding Author:
Rahul Janak Sinha, MS, MCh
C/O Dr Sheela Sharma, O/83,
Doctor's Colony, Kankarbagh, Patna 800020, Bihar, India
Tel: +91 941 500 3051
E-mail: rahuljanaksinha@rediffmail.com

Received September 2008
Accepted December 2008

MATERIAL AND METHODS

A general free-of-charge health checkup camp was advertised and mandated for all male employees aged between 40 and 60 years working in various subspecialties of surgical departments (including surgical gastroenterology, urology, neurosurgery, etc) in various capacities such as clerks, ward and operation theatre assistants, nurses, etc. This was done in order to assess andropause frequency by a standardized questionnaire and to obtain blood sample for serum testosterone estimation. We screened volunteers for any coexisting disease and excluded those having chronic liver disease, chronic kidney disease, chronic heart disease, or any other diseases or conditions requiring medications that could affect serum testosterone assay.

Ethical clearance for this study was obtained from the institutional ethics committee and was in accordance with the Declaration of Helsinki. This camp was organized for a 1-week period in April, 2007. The workers who presented in the morning would undergo the free checkup camp if they had not attended a night duty the previous night. All participants were asked to fill a form comprising of information on age, occupation, comorbid conditions, drug intake, and past illnesses. A thorough physical examination was done. Investigations deemed necessary to rule out any coexisting disease or even other investigations not related to andropause per se were done for free (eg, ultrasonography for benign prostatic enlargement, urinalysis for those complaining of burning in micturition, blood glucose estimation for diabetics complete blood count, serum creatinine estimation, liver function tests, electrocardiography, and ultrasonography of the abdomen if required).

We used an interviewer-administered vernacular version of the Saint Louis University's ADAM questionnaire (Appendix).[1,3] An interviewer who understood the significance and meaning of these questions asked the questions in *Hindi* language which is the spoken language in the northern India. Serum testosterone (total and free) level estimation was performed simultaneously using enzyme-linked immunosorbent assay (DRG International Inc, Mountainside, *New Jersey*, USA). Blood samples for this purpose were withdrawn between 8 AM to 11 AM. The reference range of serum total testosterone for men was between 2 ng/mL and 6.9 ng/mL and that of free testosterone level was 15 ± 7 pg/mL as per the standardized value with the enzyme-linked immunosorbent assay kit. The upper and lower limits of the serum testosterone might vary between different populations and also according to the laboratory kit being used for measurement. The measurement was standardized according to the information supplied by the manufacturer of this kit.

RESULTS

Of the 180 listed male workers who were between 40 and 60 years old, 170 attended the free health camp. The volunteers were informed about the plan of this camp for doing a free survey for andropause. This was done when they came to the camp in order to prevent selection/participation bias. Their consent was taken for enrolling them in the andropause survey. Of 170 participants, 157 were found eligible and were included in this study. Thirteen volunteers were excluded because of having comorbid conditions including diabetes mellitus (6 patients), hypertension (6 patients), and others (1 with vitiligo who was on intermittent phototherapy).

The mean age of the enrolled volunteers was 53.1 years (range, 40 to 60 years). The mean body weight was 64.3 kg (range, 54 kg to 78 kg) and the mean height was 167.4 cm (range, 158 cm to 180 cm). On the basis of the Saint Louis University's ADAM questionnaire, 106 of the total of 157 participants (67.5%) tested positive for symptoms of andropause (mean age, 53.5 years; range, 40 to 60 years), of whom 41 (38.7%) were found to have a serum free testosterone level lower than the normal (mean, 5.55 pg/mL; range, 3.09 pg/mL to 7.08 pg/mL) and 32 (30.2%) had a low total testosterone level (mean, 1.5 ng/mL; range, 1.1 ng/mL to 1.9 ng/mL). The remaining 33 symptomatic men had normal total and free testosterone levels (mean age, 51.8 years; range, 40 to 60 years). Fifty-one of the 157 participants were asymptomatic (32.5%) on the basis of the answers to the questionnaire, 11 of

these men (21.6%; mean age, 55.1 years; range, 46 to 60 years) were found to have low serum free testosterone levels (mean, 6.4 pg/ml; range, 4.1 pg/mL to 7.4 pg/mL) and 6 (11.8%) had low serum total testosterone levels (mean, 1.4 ng/mL; range 1.2 ng/mL to 1.9 ng/mL).

DISCUSSION

The exact prevalence of ADAM is not known; however, it is anticipated that as the life span of human beings is increasing, the prevalence of this condition is also on the rise. The Massachusetts Male Aging Study reported a crude incidence rate of 12.3 per 1000 person-years, leading to a prevalence of 481 000 new cases of ADAM per year in American men aged 40 to 69 years old.[2] The prevalence of ADAM has not been reported from most of the Asian countries and few reports exist regarding the status of ADAM in Asia.[4-6] To estimate the prevalence of this condition in India, we performed a pilot study in a small number of volunteers working in the surgical departments at our hospital. India is a conservative country and many in the age group of 40 to 60 years are not comfortable in talking about their sexual life. We had the feeling that if we announced a camp only for andropause then it might not attract enough participants and perhaps even lead to selection/participation bias. Therefore, we decided to name this camp a free general health checkup camp, but those referred were first fully informed of the program. In this manner, voluntary participation was increased while the chances of selection/participation bias (that volunteers with some sexual problems only will attend the camp) were minimized.

Of the 3 commonly used questionnaires,[1] the Saint Louis University's ADAM questionnaire was chosen because of its simplicity. This questionnaire has been tested and reported previously.[3,7] Ideally, the questionnaire should been validated in Indian population before its use, but the Saint Louis University's ADAM questionnaire has not been validated in Indian population and this is one of the weaknesses of this study.

In our study an unusually high number of volunteers, 106 of 157 (67.5%), reported symptoms of ADAM on the basis of the Saint Louis University's questionnaire. This high frequency of andropause seen in our study could be due to the nature of the questionnaire itself. The questionnaire was structured on a "yes/no" format and the volunteers did not have the scope of reporting that they had only mild symptoms. Many volunteers who had mild symptoms might have been wrongly picked up as symptomatic for andropause on the basis of this questionnaire. Some questions like "have you noticed a recent deterioration in your ability to play sports?" may not be relevant in some countries like India where most people above 40 years of age do not play sports. Similarly, many of our volunteers reported that answers to questions 2, 3, 8, and 10 were quite close to each other (Appendix). The Saint Louis questionnaire states that if the answer to question 1 or question 7 is "yes," then the patient is considered to be most probably positive for andropause. These two questions are direct and most of the patients who were positive for andropause on the basis of symptoms answered "yes" to these two questions.

On the basis of serum biochemical evaluation, 52 of 157 participants (33.1%) were found to have low free serum testosterone levels. However, the serum total testosterone levels were found to be low in 38 participants (24.2%) only. This could have happened due to the fact that normal total testosterone levels have a wide normal range and do not decline as rapidly as do free and bioavailable (free and albumin-bound) testosterone concentrations.[8-11] The more pronounced decrease in free compared to total testosterone is explained by the age-dependent increase in the binding capacity of sex hormone-binding globulin (1.2% per year). Many investigators have suggested that measurement of bioavailable and/or free testosterone is a better investigation for diagnosing andropause.[12,13] The ideal test in men suspected of hypogonadism is the measurement of free testosterone by the equilibrium dialysis method.[13] This method is difficult to perform, not automated and inaccessible to most clinicians. Measurement of free testosterone by radioimmunoassay method is widely available but unreliable.[13] We have evaluated serum testosterone levels using the

enzyme-linked immunosorbent assay which is a reliable method.

The reported prevalence of biochemical hypogonadism is about 7% in the age group younger than 60 years old and increases to 20% in those older than 60 years.[14] In the present study, biochemical hypogonadism (based on more accurate serum free testosterone levels) was observed in 52 (33.1%) out of 157 participants while 41 volunteers (26.1%) revealed both symptomatic as well as biochemical hypogonadism (positive symptoms as well as low free serum testosterone levels). The frequency of biochemical hypogonadism reported in our study (33.1%) is similar to that found in a study on 316 Canadian physicians aged 40 to 62 years. Low bioavailable testosterone levels (< 70 ng/dL) were present in 25% of these physicians; the questionnaire identified this group with a sensitivity of 88% and a specificity of 60%.[3]

Serum testosterone levels show diurnal variation and there is also substantial variation (~20%) from week to week.[15] Therefore, 2 testosterone measurements at least a week or two apart are recommended for diagnosing ADAM and starting treatment.[1] We measured serum testosterone at a single point which may have overestimated or underestimated this condition and this is another weakness of this study. Given this fact, the volunteers who were diagnosed as having ADAM were informed about the shortcomings of this study. They were advised not to start any treatment until and unless they underwent further tests to confirm the findings of this study. Also, the considerable number of patients with symptoms of hypogonadism on the basis of questionnaire but with normal serum testosterone levels found in our patients could be because of the nature of the ADAM questionnaire itself.

Another weakness of this study is the small number of participants on the basis of which it would be difficult to comment whether the findings reflect the corresponding male population in the entire country. It would suffice to state at this point that all queries cannot be answered through this pilot study alone. The frequencies were not calculated separately for individual age groups due to small numbers in such subgroups. On statistical analysis, the small numbers in individual subgroups did not justify any comment on the impact of age on the frequency of ADAM in these volunteers. The strength of this study lies in the fact that it was conducted on a well-selected population employed in the health sector. The participants were literate and provided complete information related to their medication and treatment history. They were unaware of the real purpose of this study before inclusion and they were able to give feedback regarding the problems or confusions that they had in answering the Saint Louis University's questionnaire.

Validating any questionnaire requires money, manpower, and justification for conducting such an exercise. This study perhaps lays some groundwork to conduct further studies either to validate such questionnaires in the Indian population or to estimate the prevalence in Indian men on a larger scale. The need of the hour is perhaps a questionnaire constructed with Indian population in mind which is more in sync with our social customs. Regarding biochemical indicators of ADAM, free serum testosterone levels may be a better test to diagnose ADAM.[1] Other biochemical parameters need to be discovered, which will make the task of defining andropause easier.

CONCLUSION

On the basis of this study, it seems that ADAM is prevalent in our country. Validated questionnaires and further studies may shed more light on the concept of ADAM.

ACKNOWLEDGEMENT

We would like to thank the members of the Research Cell of Chhatrapati Shahuji Maharaj Medical University (King George's Medical University), Lucknow, India for approving this research project and giving us the financial aid which made this study possible. The authors thank Dr Rupin Shah MS, MCh (consultant urologist and andrologist, MPUH, Nadiad, India) for his constant support and guidance.

APPENDIX

The Androgen Deficiency in Aging Male (ADAM) Questionnaire[1]

A positive answer represents yes to 1 or 7 or any 3 other questions

1. Do you have a decrease in libido? yes/no
2. Do you have a lack of energy? yes/no
3. Do you have a decrease in strength and/or endurance? yes/no
4. Have you lost height? yes/no
5. Have you noticed a decreased enjoyment of life? yes/no
6. Are you sad and/or grumpy? yes/no
7. Are your erections less strong? yes/no
8. Have you noticed a recent deterioration in your ability to play sports? yes/no
9. Are you falling asleep after dinner? yes/no
10. Has there been a recent deterioration in your work performance? yes/no

CONFLICT OF INTREST

None declared.

REFERENCES

1. Morales A, Morley J, Heaton JPW. Androgen deficiency in the aging male. In: Wein AJ, Kavoussi LR, Novick AC, Partin AW, Peters CA, editors. Campbell-Walsh urology. 9th ed. Philadelphia: Saunders; 2007. p. 850-62.
2. Araujo AB, O'Donnell AB, Brambilla DJ, et al. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts Male Aging Study. J Clin Endocrinol Metab. 2004;89:5920-6.
3. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239-42.
4. Li JY, Li XY, Li M, et al. Decline of serum levels of free testosterone in aging healthy Chinese men. Aging Male. 2005;8:203-6.
5. Reyes JA, 3rd, Tan DA, Quimpo JA, et al. The Philippine Male Aging Survey. Aging Male. 2004;7:227-35.
6. Ichioka K, Nishiyama H, Yoshimura K, Itoh N, Okubo K, Terai A. Aging Males' Symptoms scale in Japanese men attending a multiphasic health screening clinic. Urology. 2006;67:589-93.
7. Tancredi A, Reginster JY, Schleich F, et al. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. Eur J Endocrinol. 2004;151:355-60.
8. Vermeulen A. Clinical review 24: Androgens in the aging male. J Clin Endocrinol Metab. 1991;73:221-4.
9. 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;147:750-4.
10. Morley JE, Kaiser F, Raum WJ, et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. Proc Natl Acad Sci U S A. 1997;94:7537-42.
11. Nahoul K, Roger M. Age-related decline of plasma bioavailable testosterone in adult men. J Steroid Biochem. 1990;35:293-9.
12. Tenover JS. Declining testicular function in aging men. Int J Impot Res. 2003;15 Suppl 4:S3-8.
13. Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. Aging Male. 2002;5:74-86.
14. Vermeulen A, Kaufman JM. Ageing of the hypothalamo-pituitary-testicular axis in men. Horm Res. 1995;43:25-8.
15. Morley JE, Patrick P, Perry HM, 3rd. Evaluation of assays available to measure free testosterone. Metabolism. 2002;51:554-9.

EDITORIAL COMMENT

The paper by Goel and colleagues addressed an important but neglected issue in the field of men's health. The International Society for the Study of the Aging Male has considered the process of *andropause* as a "syndrome." This syndrome is characterized by decreased serum androgen, with or without a decreased genomic sensitivity to androgens.[1] Due to the lack of a universally accepted definition for andropause, limited ''reliable'' data exist on its real prevalence. This study has shown symptomatic andropause in 67.5% of studied men aged from 40 to 60 years, which seems very high. Different values and subtypes of measured testosterone used in different studies make it difficult to compare their results to the existing epidemiological data. Nevertheless, in a well-

conducted longitudinal study by Harman and coworkers, the reported rates for reduced levels of free testosterone were 9% for men aged from 50 to 59 years and 34% for men aged between 60 and 69 years.[2] The prevalence of hypogonadism in other studies is similar. Wishart and colleagues demonstrated that 25% of men over 65 years old have serum testosterone levels less than 300 ng/dL.[3] For detecting hypogonadism, the Saint Louis University's androgen decline in the aging male questionnaire is a valid test, but its specificity is low.[4] This tool must be coupled with a complete clinical evaluation, and the definition of hypogonadism should depend on both biochemical and functional criteria.[5] Nowadays, bioavailable testosterone testing in replacement of or addition to the traditional total testosterone and direct free testosterone assays is recommended. It more accurately reflects the clinical androgen state of the patient.[6] In addition, there is considerable interindividual and intra-individual variability in androgen levels. At least 2 samples in different days are needed to draw accurate estimation of serum androgen. Additionally, indicative threshold for hypoandrogenemia is an important issue. Usually, the lower limit of the reference range in young men is used for defining a cutoff value for hypoandrogenemia in elderly men.[7]

A low testosterone level can also be indicative of an underlying pituitary disorder; therefore, measurement of serum luteinizing hormone and follicle-stimulating hormone might be helpful for distinguishing between these two entities (true andropause and pituitary disorder).

The clinical significance of serum androgens declines in aging men is still unclear, and there is disagreement as to whether a specific syndrome of androgen deficiency or "andropause" exists. Therefore, further well-designed, and large-population-based studies in different ethnicities are needed to establish the accurate prevalence of andropause and its clinical implications in aged men.

Mohammad Reza Safarinejad

Associate Editor, Urology Journal

REFERENCES

1. Morales A, Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. Aging Male. 2002;5:74-86.
2. Harman SM, Metter EJ, Tobin JD, Pearson 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;86:724-31.
3. Wishart JM, Need AG, Horowitz M, Morris HA, Nordin BE. Effect of age on bone density and bone turnover in men. Clin Endocrinol (Oxf). 1995;42:141-6.
4. Martinez-Jabaloyas JM, Queipo-Zaragoza A, Rodriguez-Navarro R, Queipo-Zaragoza JA, Gil-Salom M, Chuan-Nuez P. Relationship between the Saint Louis University ADAM questionnaire and sexual hormonal levels in a male outpatient population over 50 years of age. Eur Urol. 2007;52:1760-7.
5. Morley JE. The need for a Men's Health Initiative. J Gerontol A Biol Sci Med Sci. 2003;58:614-7.
6. Lepage R. Measurement of testosterone and its sub-fractions in Canada. Clin Biochem. 2006;39:97-108.
7. T'Sjoen G, Goemaere S, De Meyere M, Kaufman JM. Perception of males' aging symptoms, health and well-being in elderly community-dwelling men is not related to circulating androgen levels. Psychoneuroendocrinology. 2004;29:201-14.

REPLY BY AUTHOR

As the average lifespan is increasing across the globe due to better healthcare, the entity *late-onset hypogonadism* (LOH) is being appreciated more by the physicians. Interest in this field has increased exponentially over the last decade and has led to further research and development of better tools for investigation. Leading luminaries in this field are working closer to reach common ground.[1] This means that the current set of recommendations are undergoing changes and it might be a while before consensus is reached on how to define andropause, whom to define as "andropausal," and how to treat this entity.

We used the androgen decline in the aging male (ADAM) questionnaire and assessed serum testosterone values (both total and free) to reach our conclusions; so our results are still consistent with the latest recommendations as they are based on both symptomatic as well as biochemical analyses.[1] We agree with Dr

Safarinejad that more studies on andropause in men from different ethnic backgrounds are needed. Our study was a pilot project to estimate the probable frequency of symptomatic hypogonadism in a subpopulation of urban Indian men. Hence, follicle-stimulating hormone and luteinizing hormone were not assessed. We do not have access to assays of bioactive testosterone, so it could not be assessed.

Even though symptomatic hypogonadism was higher in our study, less than half the men who were symptomatic on the ADAM scale had low testosterone levels. This is consistent with the low specificity of the ADAM questionnaire. The incidence of symptomatic LOH was 33.1% in this study. This is higher than reported by some studies[2]; but is in keeping with the findings reported by others.[3]

We sincerely hope that the current deliberations on LOH by the international community shall help in establishing a format for research which is acceptable to the majority of physicians working in this field. Comparisons of various aspects of LOH amongst men from different ethnic backgrounds then may become easier.

Rahul Janak Sinha, Vishwajeet Singh

Department of Urology, Chhatrapati Shahuji Maharaj Medical University, Lucknow, Uttar Pradesh, India

REFERENCES

1. Wang C, Nieschlag E, Swerdloff R, et al. Investigation, Treatment, and Monitoring of Late-Onset Hypogonadism in Males: ISA, ISSAM, EAU, EAA, and ASA Recommendations. Eur Urol. 2009;55:121-30.
2. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab. 2001;86:724-31.
3. Morley JE, Charlton E, Patrick P, et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism. 2000;49:1239-42.