

Validation of a Screening Questionnaire for Androgen Deficiency in Aging Males

John E. Morley, E. Charlton, P. Patrick, F.E. Kaiser, P. Cadeau, D. McCready, and H.M. Perry III

It is now well established that testosterone levels decline with age. What has not been established is whether the decline in testosterone is associated with a symptom complex. This study examined whether certain symptoms are more commonly present in males with low bioavailable testosterone (BT) levels. These were used to evaluate a questionnaire for androgen deficiency in aging males (ADAM). The validity of the ADAM questionnaire to screen for low BT was tested in 316 Canadian physicians aged 40 to 62 years. Low BT levels were present in 25% of this population. None had elevated luteinizing hormone (LH) levels. The ADAM questionnaire had 88% sensitivity and 60% specificity. When the questionnaire was administered twice 2 to 4 weeks apart to 10 men, it was determined that the coefficient of variation was 11.5%. In a second study of 34 ADAM-positive patients, 37% of those with clearly normal BT levels demonstrated some evidence of dysphoria. Finally, in 21 patients who were treated with testosterone, improvement on the ADAM questionnaire was demonstrated in 18 ($P = .002$). These data support the concept of a symptom complex associated with low BT levels in aging males. In addition, the ADAM questionnaire appears to be a reasonable screening questionnaire to detect androgen deficiency in males over 40 years of age. Copyright © 2000 by W.B. Saunders Company

BOTH CROSS-SECTIONAL¹⁻⁸ and longitudinal⁹ studies demonstrate that testosterone levels decline with age in males. This decline in testosterone is predominantly due to a failure in the function of the hypothalamic-pituitary unit, ie, secondary hypogonadism,¹⁰⁻¹⁵ although alterations in testicular function have also been demonstrated.¹⁶⁻¹⁸ Not only does the total serum testosterone concentration decline with aging, but even more dramatic decreases in the unbound hormone, free testosterone¹⁹ or bioavailable testosterone (BT),²⁰⁻²³ have been reported due to the increase in sex hormone-binding globulin that occurs with aging.¹⁹

Brown-Sequard²⁴ was the first to suggest that some of the symptoms associated with aging are due to testosterone deficiency. Schiavi et al^{25,26} found a strong correlation between the decline in enthusiasm for sex (libido) and BT levels in older males. Other correlational studies have found an association between strength, lean body mass, and memory function and the age-related decline in testosterone.^{20,27} Animal studies have supported the role of testosterone in regulating memory function,²⁸ as has a single interventional study in humans.²⁹ Other prospective interventional studies in humans have suggested that testosterone may improve muscular strength.³⁰⁻³² Testosterone therapy has been associated with a marked enhancement of libido.³³⁻³⁵ It has been suggested that the decline in testosterone may be associated with some degree of dysphoria.³⁶ Data on the relationship of the age-related decline in testosterone to osteopenia are inconclusive.^{4,27,37}

Despite a growing body of evidence that testosterone deficiency in aging males may be associated with deleterious effects, it remains controversial whether androgen deficiency in aging males (ADAM) is associated with a symptom complex similar to the well-defined menopausal symptoms associated with estrogen deficiency.³⁸ In part, the failure to recognize the ADAM syndrome has been due to the more gradual decline in testosterone that occurs in the aging male as compared with the rapid cessation of estrogen production that occurs with menopause in women.

Based on our clinical experience, we identified 10 symptoms that are commonly observed in older males with low BT levels. These symptoms were used to develop an ADAM syndrome questionnaire. This communication reports the cross-sectional validation of this questionnaire and also provides preliminary

data on the effects of testosterone therapy on this symptom complex.

SUBJECTS AND METHODS

A questionnaire was developed to examine various parameters thought to be androgen-related (Table 1). A positive result on the ADAM questionnaire was defined as an affirmative answer ("yes") to questions 1 or 7 or any 3 other questions. Three hundred sixteen Canadian physicians aged between 40 and 82 years ($52.8 \pm .5$, mean SEM) completed the questionnaire and provided a serum sample for the measurement of total testosterone (417 ± 9 ng/dL) and BT (96 ± 2 ng/dL). Luteinizing hormone (LH) levels were measured using a kit from ICN Pharmaceuticals (Costa Mesa, CA). The normal range was 2 to 16 mIU/mL.

A group of 10 males completed the ADAM questionnaire on 2 occasions 2 to 4 weeks apart to determine the coefficient of variation for the questionnaire.

In addition, 34 patients evaluated at the Saint Louis University Sexual Dysfunction Clinic completed the ADAM questionnaire as part of their routine work-up, which included the Geriatric Depression Scale.³⁹ Twenty-one of these patients had low BT levels and received treatment with 200 mg testosterone cypionate intramuscularly every 2 weeks for 3 to 4 months.

BT and total testosterone levels were measured as previously described.²⁰ The interassay and intraassay sensitivity for the BT assay was 10.4% and 5.8%, respectively.

Statistical comparisons were made by means of chi-square and paired Student *t* test where appropriate using a commercially available statistical package (Statistica, Oklahoma City, OK) and a personal computer. Cluster analysis for positive or negative questionnaires was also performed to determine if overlap existed. The studies were approved by the Saint Louis University Human Studies Committee.

From the Geriatric Research, Education and Clinical Center, St. Louis Veterans Affairs Medical Center, St. Louis; Division of Geriatric Medicine, Saint Louis University Medical School, St. Louis, MO; and Organon, Canada, Scarborough, Ontario, Canada.

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Address reprint requests to John E. Morley, MB, BCh, Saint Louis University Health Sciences Center, Division of Geriatric Medicine, 1402 S Grand Blvd, Room M238, St. Louis, MO 63104.

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Table 1. Questions Used as Part of the Saint Louis University ADAM Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

NOTE. A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

RESULTS

In the observational study of Canadian subjects, 25% had BT less than 70 ng/mL, the lowest concentration we have observed in normal men aged 20 to 45 years. The number of individuals with a BT concentration less than 70 ng/dL increased with increasing age (Fig 1). None of the subjects had an elevated LH level. The mean LH for patients with a BT less than 70 ng/dL was 3.5 ± 0.3 mIU/mL, and for those with higher levels, 3.3 ± 1 mIU/mL. The criteria for a positive questionnaire result identified 88% of men with low BT (sensitivity) with a specificity of 60%. The percentage of individuals with low BT (<70 ng/dL; low-normal, 71 to 90 ng/dL) or normal BT (>90 ng/dL) answering yes or no to each question is presented in Table 2. Positive responses were more common for each question for hypogonadal men. There were significant differences in the percentage of affirmative or negative answers in hypogonadal and normal men (BT > 90 ng/dL) for all questions except 3 and 6; the difference approached significance for the latter question (Table 2). The most common affirmative answer for individuals with low BT was in response to question 7 pertaining to the strength of penile erections (60.8% answered yes).

The coefficient of variation for repeated testing within individuals was 11.5%. Cluster analysis of positive and negative questionnaire results did not demonstrate significant overlap of the questions.

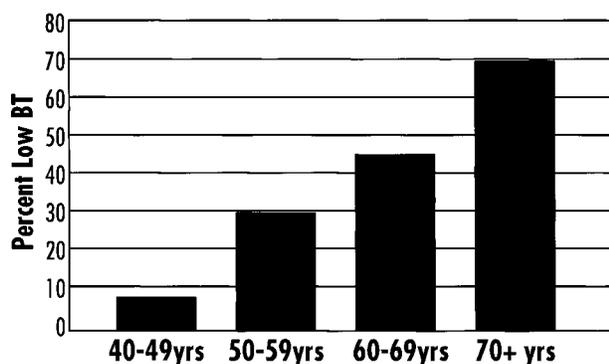


Fig 1. Twenty-five percent of Canadian physicians had lower BT (weakly bound testosterone) levels than normal young men (<70 mg/dL).

We examined the subset of individuals with a BT greater than 80 ng/dL and a positive ADAM questionnaire in the St. Louis population. Thirty-seven percent of these individuals screened positively for dysphoria/depression (10 or greater) using the Geriatric Depression Scale.

We treated 15 hypogonadal men (BT < 70 ng/dL) and 6 men with significant symptoms on the ADAM questionnaire and borderline gonadal function (BT \leq 85 ng/dL) with testosterone cypionate 200 mg intramuscularly every 2 weeks. The mean age for these men was 57.5 ± 1.6 years and the initial mean BT was 73 ± 9 ng/dL. Their mean score on the questionnaire was $5.8 \pm .5$ positive responses initially and $2.1 \pm .1$ positive responses at follow-up study ($P < .001$). The mean change in the score was $-3.8 \pm .7$ positive responses ($P = .002$). Improvement on the ADAM questionnaire was demonstrated in 18 of 21 patients ($P = .002$). Of 15 patients who answered yes to question 1, 14 responded to testosterone ($P = .003$). Of 18 patients who answered yes to question 7, 15 responded to testosterone ($P = .001$). There was a reduction from a mean of $4.3 \pm .4$ positive answers on the other 8 questions before testosterone replacement to $1.5 \pm .4$ after treatment ($P = .003$).

DISCUSSION

This study validates for the first time a noninvasive screening test for ADAM. The ADAM questionnaire showed high sensitivity, acceptable specificity, and good intrarater reliability. Testosterone therapy reversed many of the symptoms, further supporting the validity of the ADAM questionnaire. This study supports the use of the ADAM questionnaire as a clinical screening tool to identify males over the age of 40 years with hypogonadism. In addition, the ADAM questionnaire appears to be a useful tool for evaluating the therapeutic response to testosterone therapy.

This study, similar to others,¹⁻¹⁸ demonstrates the high prevalence of hypogonadism in males 40 years and older. In this study, BT identified approximately 6% more males as hypogonadal than did total testosterone, ie, nearly 25% of males with hypogonadism would not have had the diagnosis if only total testosterone was measured. Previous studies have also reported that BT or free testosterone identify a higher proportion of men as hypogonadal than total testosterone.²⁰⁻²³ This is presumably because there is an increase in sex hormone-binding globulin with aging that has been identified in both cross-sectional⁶ and longitudinal⁹ studies. Other studies have shown that the major reason for the decline in testosterone with aging is an alteration in hypothalamic-pituitary function,¹⁰⁻¹⁵ and this was confirmed in our study, wherein none of the subjects with low BT had elevated LH levels.

This study defines for the first time a symptom complex associated with declining testosterone levels in middle-aged and old males. We believe that the designation of this symptom complex as ADAM is appropriate. The response of ADAM to testosterone replacement in this study suggests that ADAM may be a disorder amenable to therapeutic intervention. This is compatible with the small number of reported therapeutic interventional studies with testosterone.^{24,30-35}

Not surprisingly, the 4 questions most associated with low BT were 2 associated with libido and strength of erections and 2 associated with muscular strength and energy. The high percent-

Table 2. Comparison of Answers on the ADAM Questionnaire (%) in Males With Low Versus Normal BT Levels

Question No.	Group 1 (BT <71 ng/dL)		Group 2 (BT 71-90 ng/dL)		Group 3 (BT >90 ng/dL)		P	
	Yes	No	Yes	No	Yes	No	1 v 2 and 3	1 v 3
1	48.1	51.9	37.1	62.9	30.4	69.6	.01	.01
2	49.4	50.6	44.9	55.1	31.8	68.2	.05	.01
3	46.8	53.2	46.1	53.9	42.6	57.4	—	—
4	21.5	78.5	14.6	85.4	10.1	89.9	.05	.01
5	35.4	64.6	25.8	74.2	23.6	76.4	.05	.05
6	38.0	62.0	29.2	70.8	26.4	73.6	.01	.06
7	60.8	39.2	37.1	62.9	41.9	58.1	.01	.01
8	46.8	53.2	33.7	66.3	30.4	69.6	.01	.01
9	41.8	58.2	34.8	65.2	27	73.0	.05	.05
10	20.3	79.7	16.9	83.1	10.1	89.9	.100	.05

age of positive answers to the question concerning falling asleep after dinner is of historical significance, as this was one of the symptoms Brown-Sequard²⁴ had suggested to be associated with his “hypogonadism.”

Previous studies have suggested that depression can be associated with disturbances in potency and libido.^{36,40,41} It has also been suggested that depression may result in decreased testosterone levels secondary to an inhibition of the hypothalamic-pituitary axis.³⁶ Thus, it is not surprising that a number of false-positives to the ADAM questionnaire were associated with scores on the Geriatric Depression Scale in a range associated with dysphoria/depression. Therefore, it would seem appropriate to check for depression in persons with an ADAM questionnaire. However, a positive score for depression does not rule out the coexistence of hypogonadism.

Clinically, we have noted a number of hypogonadal older

males who have lost significant height. We have found that this is usually associated with osteopenia. However, many of the patients are unaware of their height loss until it is measured in the clinic. This may explain the relatively low response to the question, “Have you lost height?”, in males with hypogonadism. The evidence that the decline in testosterone with aging causes osteopenia is not very robust, and the final proof of this component must await well-designed clinical interventional trials.^{4,27,37}

In conclusion, the studies reported here have validated a screening questionnaire for identifying middle-aged and older males with testosterone deficiency. Furthermore, these findings define a symptom complex associated with the age-related decline in testosterone that may be amenable to therapeutic intervention. It is suggested that this symptom complex defines the ADAM syndrome.

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