

Performance of the Androgen Deficiency in Aging Male questionnaire for the clinical detection of androgen deficiency in black sub-Saharan African men with Type-2 diabetes mellitus

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Background: The Androgen Deficiency in Aging Male (ADAM) questionnaire is increasingly popular for evaluation of androgen deficiency (AD) in sub-Saharan African men with type 2 diabetes mellitus (DM). However, its reliability in this population is unknown.

Methods: Total testosterone < 8 nmol/L was used as the gold standard for diagnosis of AD in this cross-sectional survey of 200 type 2 DM males aged 30–69 years. Participants also completed the Saint Louis University ADAM questionnaire whereby AD was diagnosed by a 'yes' answer to question 1 (reduced libido) or 7 (erectile dysfunction) or any other three questions. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of the ADAM tool were computed.

Results: The mean age of the participants was 58.0 ± 8.8 years. A total of 142 subjects (71.0%) had AD based on the ADAM questionnaire. However, AD was biochemically confirmed in 59 subjects (29.5%). The ADAM questionnaire rendered a sensitivity of 88.1%, specificity of 44.7%, PPV of 50.0%, NPV of 85.7% and accuracy of 61.4%.

Conclusion: Despite an impressive sensitivity, the low specificity and overall accuracy of the ADAM questionnaire makes it unreliable for the detection of AD in sub-Saharan African men with type 2 DM.

Keywords: ADAM, Africa, androgen, Nigeria, testosterone, type 2 diabetes

Introduction

Age-related androgen deficiency (AD) in males is well recognised in the literature.^{1,2} It is estimated that testosterone declines at a rate of about 0.5–2% per year during normal ageing, starting from the fifth decade.¹ Type 2 diabetes mellitus (DM) is independently associated with testosterone deficiency, and accelerates the age-related decline in androgens that naturally accompanies the ageing process.^{3,4}

Androgen deficiency is known to be associated with several adverse consequences including sexual disorders, mood changes (irritability and depression), cognitive decline, reduced muscle and bone mass leading to increased fracture risk, poor quality of life and mortality.^{5–7} Therefore AD constitutes an additional substantial burden in persons with diabetes. More recently, male androgen deficiency has been recognised as an independent risk factor for coronary artery disease.⁸ These underscore the need for prompt detection and treatment of this condition.

Although measurement of serum testosterone has been the gold standard for the diagnosis of AD, testosterone assays are not readily available, especially in resource-poor settings with inadequate healthcare facilities. Consequently, efforts have been made to develop and validate simple screening questionnaires for the clinical detection of AD.^{9–11} These questionnaires are often based on symptom complexes that are known to be associated with low testosterone concentrations.

Of all the available screening questionnaires for AD, the Saint Louis University Androgen Deficiency in Aging Male (ADAM)

questionnaire is the most widely used.⁹ Although it was originally developed in a non-diabetic Caucasian population, the ADAM questionnaire is widely used in Africans and diabetics despite absence of evidence of its reliability in this population.^{12,13} This study was aimed at evaluating the accuracy of the ADAM questionnaire as a tool for clinical detection of AD in sub-Saharan African men with type 2 DM.

Subjects and methods

Males aged 30–69 years diagnosed with type 2 DM were included in this cross-sectional survey. Participants were purposely and consecutively recruited from the diabetes clinic of Obafemi Awolowo University Teaching Hospital, Ile-Ife, Nigeria. The hospital's Research and Ethics Committee approved the protocol while each patient gave written consent. Exclusion criteria were previous/current therapy with androgens or androgen antagonists, acute febrile illness in the last one week, known or suspected chronic debilitating illnesses including chronic heart failure, chronic liver disease, chronic renal failure, tuberculosis, chronic obstructive pulmonary diseases, acquired immunodeficiency syndrome and malignancy. Relevant socio-demographic and diabetes-related information were documented.

Clinical evaluation of androgen deficiency

Participants completed the original version of the ADAM questionnaire.⁹ It consists of 10 items describing the most common symptoms observed in persons with AD and covers three dimensions, i.e. energy, mood and sexual disorders. A positive ADAM test is made if the participant answers 'yes' to any

of the sexual questions (decreases in libido or strength of erections) or any other three questions.

Laboratory evaluation

Venous blood samples were drawn between 8.00 and 10.00 a.m. in a plain specimen bottle on the day of screening. The clotted specimen was centrifuged at 3000 revolutions per minute for 5 minutes and the serum extracted and frozen. It was used for measurement of total testosterone (TT) by enzyme-linked immunosorbent assay technique (Fortress Diagnostics, Antrim, UK). Diagnosis of AD was based on the joint clinical practice guideline of the International Society of Andrology, International Society for the Study of Aging Male and the European Urology Association, which defined AD as TT < 8 nmol/L.¹⁴

Statistical analysis

Analysis was done with Statistical Package for Social Sciences® software (version 17.0; SPSS Inc. Chicago, IL, USA). Data were expressed as means ± standard deviations (SD) or frequencies and percentages as appropriate. Differences between categorical variables were tested by chi-square while an independent t-test and ANOVA were employed for continuous variables as appropriate. The sensitivity (the probability that a patient with TT < 8 nmol/L has a positive ADAM test), specificity (the probability that a patient with TT > 8 nmol/L has a negative ADAM test), positive predictive value (PPV) (the probability that a patient with a positive ADAM test has TT < 8 nmol/L) and negative predictive value (NPV) (the probability that a patient with a negative ADAM test has TT > 8 nmol/L) of the ADAM questionnaire were determined. The overall efficiency of ADAM, which was defined by the percentage of subjects who were correctly classified as either hypogonadal or normal, was also determined. Similar calculations were also independently determined for the items in the sexual domain of the ADAM questionnaire (items 1 and 7). Statistical significance was established at $p < 0.05$.

Results

A total of 200 participants with a mean age of 58.0 ± 8.8 years (range 30–69 years) completed the study. Based on the ADAM questionnaire, 142 subjects (71.0%) had androgen deficiency and this frequency increased significantly with increasing age (Table 1).

Using TT < 8 nmol/L, AD was confirmed in 59 (29.5%) subjects. Testosterone levels progressively declined with age, from 21.5 ± 7.5 nmol/L in the age range 30–39 years to 11.8 ± 6.7 nmol/L in the age range 60–69 years. Compared with subjects in the age range 30–39 years, TT declined to about 91.1% in the age category 40–49 years, 72.7% in the age category 50–59 years and 55.1% in the age group 60–69 years and this trend was statistically significant (ANOVA, $p < 0.001$) (Table 2).

Table 1. Prevalence of androgen deficiency symptoms according to age

Age group (years)	ADAM	
	Positive, n (%)	Negative, n (%)
30–39	4 (2.8)	6 (10.3)
40–49	15 (10.6)	10 (17.2)
50–59	40 (28.2)	19 (32.8)
60–69	83 (58.5)	23 (39.7)

Notes: Chi-square = 9.175, $p = 0.027$.

Table 2. Changes in serum testosterone in relation to age

Age group (years)	n	TT (mean ± SD)	% Change	F	p-value
30–39	10	21.5 ± 7.5	Reference	11.868	< 0.001
40–49	25	19.5 ± 8.9	91.1		
50–59	59	15.6 ± 7.9	72.7		
60–69	106	11.8 ± 6.7	55.1		

Note: TT = total testosterone.

Table 3. Testosterone levels of subjects with and without symptoms of androgen deficiency in the ADAM questionnaire

ADAM symptom	TT (nmol/L)		t	p-value
	Yes	No		
Decreased libido	11.0 ± 7.7	16.7 ± 7.4	5.263	< 0.001
Lack of energy	11.1 ± 6.1	16.6 ± 8.4	5.063	< 0.001
Decrease in strength/endurance	15.3 ± 8.2	13.9 ± 7.9	1.214	0.226
Lost height	10.2 ± 5.6	14.6 ± 8.0	1.617	0.107
Decreased enjoyment of life	13.3 ± 7.6	15.1 ± 8.2	1.521	0.130
Often sad or grumpy	11.4 ± 8.0	15.2 ± 7.8	2.817	0.005
Erectile dysfunction	12.0 ± 7.2	18.2 ± 7.8	5.719	< 0.001
Recent deterioration in sporting ability	13.3 ± 7.4	14.9 ± 8.2	1.181	0.239
Falling asleep quickly after dinner	14.0 ± 7.8	14.7 ± 8.2	0.632	0.528
Recent deterioration in work performance	16.7 ± 9.2	14.0 ± 7.8	1.628	0.105

Notes: Data are mean ± SD. TT = total testosterone.

Testosterone levels were compared according to the presence or absence of the symptoms of androgen deficiency as contained in the ADAM questionnaire. As shown in Table 3, TT did not differ significantly between those who had and those who did not have most of the symptoms. Exceptions are reduced libido (11.0 ± 7.7 vs. 16.7 ± 7.4 , $p < 0.001$), lack of energy (11.1 ± 6.1 vs. 16.6 ± 8.4 , $p < 0.001$), grumpiness (11.4 ± 8.0 vs. 15.2 ± 7.8 , $p = 0.005$) and erectile dysfunction (12.0 ± 7.2 vs. 18.2 ± 7.8 , $p < 0.001$).

The ADAM questionnaire rendered a sensitivity of 88.1%, specificity of 44.7%, PPV of 50.0%, NPV of 85.7% and overall accuracy of 61.4% (Table 4). As shown, each item in the sexual domain (items 1 and 7) showed better diagnostic performance than the complete ADAM questionnaire although they both demonstrated lower sensitivities. Reduced libido had the highest specificity of 75.5%, PPV of 64.1% and accuracy of 73.2%.

Discussion

It is now well established that androgen deficiency frequently complicates type 2 diabetes.^{3,4,12} Although the exact pathophysiological mechanism remains poorly understood, hypothalamic insulin resistance has largely been blamed for this abnormality.^{14,15} Type 2 DM is also more prevalent in the older populations in whom age-related decline in serum testosterone notably occurs. The Endocrine Society recommends routine screening of all men with type 2 DM for AD due to the high frequency of this condition in this group of patients.¹⁶

Table 4: Diagnostic efficiency of the ADAM questionnaire and its sexual domain

	TT		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
	Low	Normal					
<i>ADAM</i>							
Positive	52	52	88.1	44.7	50.0	85.7	61.4
Negative	7	42					
<i>Reduced libido</i>							
Yes	41	23	69.4	75.5	64.1	79.8	73.2
No	18	71					
<i>Erectile dysfunction</i>							
Yes	47	44	79.7	53.2	51.6	80.6	63.4
No	12	50					

Notes: TT = total testosterone, PPV = positive predictive value, NPV = negative predictive value.

In resource-poor settings such as sub-Saharan Africa, routine testosterone assays in men diagnosed with type 2 DM is not feasible. Therefore, the availability of a cheap, user-friendly and yet reliable clinical instrument for the detection of AD in diabetic men would be of immense benefit. The Androgen Deficiency in Aging Male questionnaire is widely used in Africa but its reliability has not been established.

In this cross-sectional survey, we evaluated the usefulness of the ADAM tool for the detection of AD in a population of mostly middle-aged and elderly Nigerian men with type 2 DM. With a diagnostic accuracy of 61.4%, the ADAM questionnaire misclassified nearly 40% of subjects in whom it was applied, making it an unreliable tool for the identification of AD in this group of patients. Although the ADAM instrument demonstrated a satisfactory sensitivity of 88.1%, its low specificity of 47% suggests that it cannot be used as a surrogate for biochemical determination of serum testosterone in evaluation of AD in type 2 diabetic males. This poor performance of the ADAM questionnaire has been reported by many authors in different patient populations. For instance, Chu *et al.*,¹⁷ in a study of nearly 800 non-diabetic Chinese men aged 18–89 years who were screened for AD using the ADAM questionnaire, reported a similarly high sensitivity of 86% and low specificity of 40% based on bioavailable testosterone (BT). The PPV and NPV of 50% and 85.7% respectively that were observed in this study were similar to those reported in the said study (46% and 82% respectively). A previous large Belgian study involving over 5000 subjects aged 50–70 years, which defined AD based on free testosterone (FT) level < 7 ng/dl, had observed a similar sensitivity of 81% for the ADAM instrument.¹⁸ However, it also reported a much lower specificity of 21.6% and concluded that the ADAM questionnaire lacked adequate specificity to be relied on for the detection of AD. Morley *et al.*¹⁹ in the United States observed similar trends regarding the ADAM questionnaire, reporting a high sensitivity of 97% and low specificity of 30%. Recently, some Taiwanese researchers evaluated the performance of two popular screening questionnaires—the ADAM and the Aging Males Symptoms (AMS) scale—in a cohort of middle-aged men.²⁰ Like our study, total testosterone was used to define AD. The authors reported an even lower sensitivity of 72%, specificity of 26.5%, PPV of 21.8% and NPV of 76%. This lower sensitivity may be due to the higher testosterone cut-off value of 10.4 nmol/L used to define AD in that study compared with 8.0 nmol/L as used in our study.

It is noteworthy that all the cited studies were conducted among non-diabetic populations. To our knowledge, there are no published data on the reliability of the ADAM questionnaire specifically in diabetic subjects elsewhere. Interestingly, our findings did not differ significantly from those of other authors, and confirm earlier reports on the disappointing performance of the ADAM tool. Our findings also suggest that the ADAM questionnaire did not discriminate between diabetics and non-diabetics.

The ADAM questionnaire evaluates three main domains, namely, energy, mood and sexual function. A critical look at these domains shows that they are prone to being affected by several other illnesses besides androgen deficiency. Therefore, the poor specificity of the ADAM instrument is not surprising. This is even more so in persons with diabetes such as our study population in whom disorders of energy, mood and sexuality are common even in the presence of normal circulating androgen concentrations and could be accounted for by hyper/hypoglycaemia, cardiovascular and renal diseases, adverse effects of medications and psychological problems including anxiety and depression. For instance, the prevalence of clinically significant depression among Nigerians with DM has been reported to be as high as 30%.²¹ Similarly, erectile dysfunction is a common complication of DM, occurring in over 70% of men with type 2 DM.²² Therefore, it is deducible that the non-specific nature of the components of the ADAM questionnaire may be responsible for its poor overall efficiency in identifying male androgen deficiency.

Findings from this study suggest that the sexual domain of ADAM alone may be more reliable than the complete questionnaire. We observed that reduced libido alone had a reasonably higher specificity of 75.5% and overall accuracy of 73.2% compared with 44.7% and 61.4% respectively demonstrated by the complete ADAM questionnaire (see Table 4). Similarly, erectile dysfunction alone had a better specificity and accuracy of 53.2% and 63.4% respectively compared with the complete questionnaire. Furthermore, subjects who answered 'yes' to the two questions in the sexual domain (items 1 and 7) had significantly lower testosterone concentrations than those who answered 'no' ($p < 0.001$ respectively). Blumel *et al.*²³ had also reported better performance of the sexual items of the ADAM instrument than the complete questionnaire and attributed this finding to the high prevalence of psychological symptoms in the complete questionnaire, which are

highly non-specific. With a uniformly high NPV of over 80% observed in both our study and those of other authors,^{17–20} it appears that the most important usefulness of the ADAM test is the identification of subjects in whom further evaluation by biochemical testing is unwarranted. This suggests that a negative ADAM test is more useful than a positive one in clinical practice.

In conclusion, despite having satisfactory sensitivity, the low specificity and poor overall accuracy of the ADAM questionnaire in this study means it cannot be used as a surrogate for biochemical assay of testosterone in the detection of androgen deficiency in sub-Saharan African men with type 2 DM. Owing to scarce healthcare resources in our setting, we recommend that sub-Saharan African men with type 2 DM in whom clinical suspicion of AD exists should be initially screened with the ADAM instrument and those who test negative may not undergo further testing while those who test positive should have testosterone measurement to confirm their androgen status. Furthermore, the presence of reduced libido should be considered a high risk factor for AD requiring proper evaluation in view of the close association between low libido and AD, as well as its high specificity in detecting androgen deficiency.

The limitations of this study need to be highlighted. First, free or bioavailable testosterone would be more accurate in evaluating AD than total testosterone as used in this study since the former represents the biologically active testosterone fraction. An alternative would have been to measure sex hormone binding globulin and albumin to calculate free testosterone index. However, this could not be done owing to cost constraints. Furthermore, the small sample size means that the findings in this study should be interpreted with caution and may not be generalised to black sub-Saharan African men with type 2 DM.

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