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RESEARCH

The prevalence and association of low testosterone levels in a South African male, diabetic, urban population

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Background: According to the literature, low serum testosterone levels are associated with diabetes mellitus. No or minimal data exist for its prevalence or predictors in South Africa.
Design: This was a cross-sectional study.
Setting: The setting was an academic centre, i.e. the University of Pretoria and Steve Biko Academic Hospital Diabetes Clinic.
Subjects: A total of 150 consecutive male patients aged 50 years and older with diabetes mellitus were selected using convenience sampling.
Outcome measures: The patients were evaluated for diabetes control and complications, and for hypogonadism symptoms. Early-morning serum testosterone levels were determined.
Results: The prevalence of androgen deficiency symptoms was 94.7%. Some 50% of the men had low total testosterone levels. Using multivariate logistic regression, the significant factors associated with low total testosterone were waist circumference and known cardiovascular disease. The prevalence of symptoms of androgen deficiency was very high; 94.7% of the patients reported a significant number of symptoms listed on the Androgen Deficiency in the Aging Male questionnaire.
Conclusion: This study confirms the high prevalence of low testosterone levels in diabetic male patients in a tertiary setting. Universal screening remains controversial owing to uncertainty regarding the risks and benefits of testosterone therapy in this population group. Predictors of low testosterone levels were identified.

Keywords: diabetes mellitus, hypogonadism, testosterone

Introduction

Male hypogonadism is a clinical condition, consisting of both the symptoms and biochemical evidence of a low testosterone level. A condition called testosterone or androgen deficiency syndrome has been described with advancing age.[1,2] The prevalence of male hypogonadism varies in the different populations and age groups studied. Its prevalence increases in male patients with diabetes mellitus, but minimal data are available on South African men with this condition.

Men with obesity, metabolic syndrome and type 2 diabetes often have low total and free testosterone, and low sex hormone binding globulin.[3–6] Low testosterone levels in men in the Rancho Bernardo study were predictive of insulin resistance and incident type 2 diabetes in older adults.[7] The nature of the relationship between type 2 diabetes mellitus and low testosterone levels remains unclear. A relationship between low serum testosterone levels and obesity, and the fact that this relationship predisposes these men to develop the metabolic syndrome, insulin resistance and type 2 diabetes, has been demonstrated in several studies, including the Massachusetts Male Aging Study.[1,3,8–10] Low testosterone levels could also be a consequence of diabetes mellitus, but even young men with type 2 diabetes and newly diagnosed type 2 diabetic patients have a high prevalence of hypogonadotropic hypogonadism.[11] A low testosterone level could also just be a biomarker that coexists with diabetes because of mutual risk factors, such as obesity and advancing age.[3,5]

It was found in a previous study that at least 25% of men with type 2 diabetes had subnormal testosterone levels, with inappropriately low luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations, indicative of hypogonadotropic hypogonadism.[11] A small percentage had subnormal testosterone levels with elevated LH and FSH concentrations, implying primary hypogonadism. Hypogonadotropic hypogonadism is the most common picture found in hypogonadal diabetic men.[11,12] One study found a prevalence of 33% of low free testosterone in type 2 diabetic men.[13]

Obesity can play a role in the pathophysiology of both hypogonadism and type 2 diabetes. Obesity is associated with hypogonadotropic hypogonadism. Thus, it is possible that this precedes diabetes.[11,14] Obesity is a proinflammatory state.[3] Visceral fat produces inflammatory cytokines, adipokines and other proinflammatory factors, such as interleukin (IL)-6, IL-1β, tumour necrosis factor-alpha, plasminogen activator inhibitor-1, angiotensinogen, vascular endothelial growth factor and serum amyloid A. Obesity also leads to an increased release of oestrogen and free fatty acid. These factors can all potentially contribute to the suppression of the hypothalamus–pituitary–gonadal axis, and can lead to androgen deficiency.[15]

There might also be a direct effect of testosterone on insulin sensitivity, with testosterone deficiency leading to insulin resistance.[1,9,16] Interactions between visceral adiposity and low testosterone levels through proinflammatory factors can result in insulin resistance and vascular endothelial dysfunction.[3] These can be potential causal factors for increased erectile dysfunction and cardiovascular disease. Leptin resistance at the hypothalamic-pituitary and testicular levels can also contribute to lowered testosterone levels.[17]

The complications of hypogonadism are numerous and varied, from impairment of quality of life to effects on mortality. Type 2 diabetic men with low testosterone levels have been found to have a high prevalence of symptoms of hypogonadism, such as erectile dysfunction, low libido and fatigability.[14,18]

Method

Setting

The study was performed in an academic centre, i.e. Steve Biko Academic Hospital Diabetes Clinic, University of Pretoria. This is a tertiary diabetes clinic in a state hospital. The University of Pretoria Ethics Committee approved the study (213/2011).

Subject selection

A total of 150 consecutive male patients aged 50 years and older with diabetes mellitus were selected using convenience sampling.

Research procedures

Information was obtained from the patients themselves, their hospital and clinic files, the hospital laboratory system, and from a questionnaire that the patients completed.

The demographic variables, such as the age, race, smoking history and employment status, of the patients were recorded.

Clinical variables, including the type of diabetes mellitus and the time since diagnosis, as well as the presence of hypertension and the time since diagnosis, were recorded. A previous history of a stroke, myocardial infarction, amputation, foot ulceration, cataracts, revascularisation, nephropathy or laser therapy of the eyes was obtained. Blood pressure was taken and averaged with the last recorded value, body mass index (BMI) was calculated and waist circumference (WC) measured. Current medications that the patients were using were recorded.

Patients completed the Androgen Deficiency in the Aging Male (ADAM) questionnaire.[19,20] The ADAM questionnaire consists of 10 questions that evaluate the kind and severity of low testosterone symptoms. A diagnosis of ADAM was suspected if a 'yes' answer was provided to questions 1 and 7, or to any other three questions. Patients were categorised as being ADAM-positive or ADAM-negative.

A peripheral neuropathy questionnaire (modified Neuropathy Symptom Score) was also completed.[21] This questionnaire consists of five questions on the symptoms of peripheral neuropathy. Patients could answer 'no', 'yes', and grade it by answering 'worse at night'.

The World Health Organization's Rose Angina Questionnaire can be used to diagnose intermittent claudication.[22] It consists of nine questions, and intermittent claudication was diagnosed or ruled out based on the patient's choice out of two possible answers. The questionnaires were chosen for their simplicity and brevity, although none of them were validated in a South African population.

Laboratory measurements

Biochemical variables included routine tests, such as a serum creatinine, serum low-density lipoprotein (LDL) value and haemoglobin A_{1c} (HbA_{1c}). Urine for an albumin/creatinine ratio was collected as a random spot urine specimen after exclusion of a possible urinary tract infection using a urine dipstick. Total testosterone non-routine tests were requested. Blood was collected in the fasting state between 7h:00 am and 10:00 am in clotting tubes following venepuncture, and was immediately refrigerated. It was transported to the laboratory (Dr WJH Vermaak Inc.) for analysis on the same day. The Roche® total testosterone assay was used on the Cobas® 6000 analyser (Roche Diagnostics, Rotkreuz, Switzerland). The laboratory-specific reference range of total testosterone for males aged 50 years and older is 9.9–27.8 nmol/l.

Data analysis

Data were analysed with Stata® 12 (Stata Corp, College Station, TX, USA). Exposure between cases and non-cases was compared using appropriate tests for continuous and categorical data. Logistic regression was utilised to determine predictors of outcome with tests of calibration and validation, as required. Logistic regression was performed to evaluate the relationship between demographic variables, clinical variables, biochemical variables, the different health-related questionnaires, and the outcome (low or normal testosterone levels), to determine which variables to use in the multivariate model. The outcome variable 'testosterone' was modelled as a dichotomous variable (low or normal). This was carried out for simplicity.

Variables with a p-value < 0.25 were entered into a multivariate model with manual backward elimination, based on the p-values in the model. Variables were dropped if the p-value was nonsignificant (< 0.05). Sensitivity, specificity, and the positive and negative predictive values were calculated. To determine the calibration of the final model, receiver-operating characteristic (ROC) analysis was performed with calculation of the c-statistic. Tenfold cross-validation of the area under the ROC curve was used for validation.

Results

Table 1 shows patients' clinical and biochemical demographic characteristics at baseline. The mean was reported for data that were normally distributed, with the standard deviation (SD). A median was reported for data with a skew distribution, with an interquartile range (IQR) from the 25th–75th percentile.

In all, 91% of the patients had type 2 diabetes mellitus, and the mean age was 62 years (SD 7.9 years). Just over half of the patients were white (53%) and 30% were black. The mean diabetes duration was 15 years (SD 8.7 years). Some 95% of the patients had previously been diagnosed with hypertension, but this was relatively well controlled with a mean systolic blood pressure of 134 mmHg (SD 15.5 mmHg) and mean diastolic blood pressure of 77 mmHg (SD 9.3 mmHg). The patients were obese, with a mean BMI of 31 kg/m^2 (SD 5.37 kg/m^2) and a mean WC of 112 cm (SD 16.4 cm). Sixty-six per cent of the patients were current (24%) or past (42%) smokers (not shown).

The median serum creatinine was 96 µmol/l (IQR 79–133 µmol/l). The patients' diabetes was better controlled than expected, with a median HbA_{1c} of 7.9 mmol/mol (IQR 6.8–9.3 mmol/mol). The mean LDL was above target at 2.33 mmol/l (SD 0.7 mmol/l), and the median triglycerides (TGs) was 1.90 mmol/l (IQR 1.20–2.50 mmol/l). The median serum total testosterone was 9.88 nmol/l (IQR 7.04–14.13 nmol/l).

Forty-one per cent of the patients were known to have cardiovascular disease and 6.7% intermittent claudication. Microvascular complications were common, with symptoms of peripheral neuropathy present in 43% of the study population, microalbuminuria in 48% of the patients, and proliferative diabetic retinopathy in 25%. Present or past cataracts affected almost 59% of the patients.

Table 1: Baseline characteristics of the patients (the clinical and biochemical variables)

Variable	*n* (%)	Mean (SD)	Median (IQR)
Type of diabetes mellitus			
Type 1	13 (8.7)		
Type 2	137 (91.3)		
Race:			
White	79 (52.7)		
Black	45 (30.0)		
Coloured	15 (10.0)		
Asian	11 (7.3)		
Co-morbidities and complications			
Hypertension	142 (94.7)		
Past or present cardiovascular disease	61 (40.7)		
Known to have proliferative diabetic retinopathy	38 (25.3)		
Significant peripheral neuropathy present	64 (43.2)		
Intermittent claudication (Rose questionnaire)*	10 (6.7)		
Present or past cataracts	86 (58.5)		
Microalbuminuria present	72 (48.0)		
Other			
Age (years)		62 (7.9)	
Diabetes duration (years)		15 (8.7)	
Body mass index (kg/m^2)		30.7 (5.37)	
Waist circumference (cm)		112 (16.4)	
Medication:			
Insulin	127 (84.7)		
Metformin	96 (64.0)		
Statins	140 (93.3)		
Diuretics	123 (82.0)		
Serum creatinine			96 (79–133)
Laboratory tests			
HbA_{1c} (mmol/mol)			7.9 (6.8–9.3)
Low-density lipoprotein (mmol/l)		2.33 (0.70)	
Serum total testosterone (nmol/l)			9.88 (7.04–14.13)
Low total testosterone (nmol/l)	75 (50.0)		

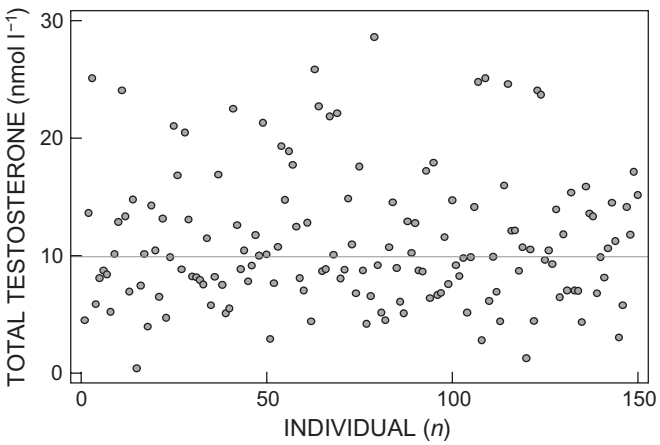
* = World Health Organization's Rose Angina Questionnaire.
HbA_{1c} = haemboglobin A_{1c}, IQR = interquartile range, SD = standard deviation.

Eighty-five per cent of the patients were on insulin therapy. Metformin was prescribed to 64% of them. Statin usage was high at 93%, and diuretics were prescribed to 82% of the study population. Low serum total testosterone levels were present in 50% of the patients.

Figure 1 is a scatter plot of the individual total testosterone values.

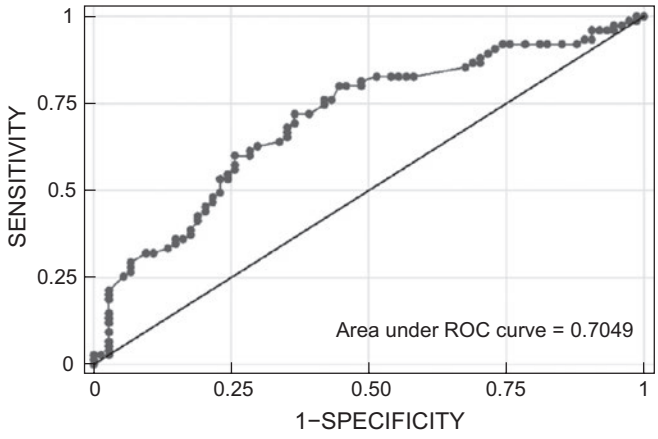
As demonstrated in Table 2, univariate associations of a low total testosterone that were statistically significant (p-value < 0.05) were BMI, WC, known cardiovascular disease and units of insulin used per day.

Table 3 shows the statistically significant multivariate associations of a low total testosterone, i.e. WC and known ischaemic heart disease. The statistically significant multivariate associations were used to create a prediction model and ROC curve (Figure 2).



Note: The horizontal line represents a lower cut-off value of 9.9 nmol/l.

Figure 1: Scatter plot of the individual total testosterone values.



Note: ROC = receiver operating characteristic.

Figure 2: Receiver-operating characteristic curve (a model for low total testosterone).

Table 4 summarises the areas under the ROC curve, before and after cross-validation. By using the model to predict low total testosterone, the area under the ROC curve was 0.70, i.e. it just reached an acceptable discrimination level. The sensitivity was 67% and the specificity was 65%. The positive predictive value was 66%, with a similar negative predictive value.

The prevalence of symptoms of androgen deficiency was very high. Ninety-five per cent of the patients reported a significant number of symptoms on the ADAM questionnaire.

The sensitivity to identify those with low total testosterone was very high at 95%, but the trade-off was a low specificity of 5%. The positive and negative predictive values were both 50%, and thus not useful.

Discussion

The prevalence of low testosterone levels was higher than those reported in the literature.[6,11–14] Half of the men had low total testosterone levels. This could be because our diabetic population had multiple co-morbid diseases and advanced diabetic complications, which can all influence testosterone levels, and they were older (a mean age of 62 years) than patients in other studies. Novel predictors of low testosterone levels could not be identified in this study, and were very similar to those reported in the literature.[3,5,9,12] When statistical measures were considered, the prediction model created from the significant multivariate associations did not perform well. Only 66% of the participants were correctly classified as having low total testosterone levels.

The prevalence of androgen deficiency symptoms was 94.7% using the ADAM questionnaire. This was a much higher prevalence than that reported in the literature.[12] The almost universal presence of these symptoms, even in patients with normal testosterone levels, made this questionnaire less useful for screening purposes. Most of the questions are relatively non-specific regarding symptoms, such as a lack of energy, being sad or ill-tempered, or experiencing a decreased enjoyment of life, strength or work performance. These symptoms can be present in many other chronic diseases and, as demonstrated, our population had numerous co-morbidities. Some of the questions focused on erectile dysfunction. There are multiple other contributing factors to this condition in diabetic patients, such as medication, neuropathy and vasculopathy.

There were several limitations to the study. It was conducted in a tertiary outpatient diabetic clinic, where most of the patients had complications of their disease and numerous co-morbid conditions. Therefore, the results cannot be generalised to the majority of diabetic patients who follow-up at primary healthcare facilities.

Patient selection bias was to some degree minimised, but not totally eliminated, by enrolling 150 consecutive patients. For example, most rural patients arrived regularly after 10:00 am at the clinic, which was too late for them to be included in the study since blood tests had to be performed in the morning. A limited number of Asian and coloured patients were included, which would make the results more difficult to interpret in these population groups.

Some of the information was subjectively obtained from patients without external collaboration, such as a history of ischaemic heart disease. Only proliferative diabetic retinopathy (either objectively observed, documented in the ophthalmology notes, or a history of laser therapy or haemorrhage provided by the patient) was recorded, owing to multiple examiners with different levels of expertise.

Table 2: Summary of univariate analysis, showing statistically significant variables with total testosterone

Variable	Normal total testosterone	Low total testosterone	*p*-value
Body mass index (kg/m^2) (mean SD)	29.4 (4.9)	32 (5.5)	0.004
Waist circumference (cm) (mean SD)	108 (14.1)	117 (17.3)	< 0.001
Known cardiovascular disease (*n*, %)	22 (29.3)	39 (52.0)	0.005
Units of insulin per day (mean SD)	50 (42.7)	69 (55.8)	0.022

Note: SD = standard deviation.

Table 3: Statistically significant multivariate associations of a low total testosterone

	Multivariate associations				
Low total testosterone	**OR**	**SE**	**95% CI (lower limit)**	**95% CI (upper limit)**	***p*-value**
Waist circumference	1.04	0.01	1.01	1.06	0.003
Ischaemic heart disease	2.18	0.78	1.09	4.39	0.029

Notes: CI = confidence interval, OR = odds ratio, SE = standard error.

Table 4: Summary of the tenfold cross-validation of the area under the receiver-operating characteristic curve

Model	Tenfold cross-validation	ROC area	SE	95% CI	
				Lower limit	Upper limit
Low total testosterone	Before	0.705	0.043	0.621	0.789
	After	0.678	0.044	0.591	0.764

Notes: CI = confidence interval, ROC = receiver-operating characteristic, SE = standard error.

Funding prohibited us from obtaining confirmatory testosterone levels and serum albumin levels to calculate the bioavailable testosterone, and serum LH levels to distinguish between primary and secondary hypogonadism. The questionnaires used have not been validated in a multi-ethnic South African setting.

A few questions remain unanswered. First, it is unclear which patients to screen for hypogonadism. The Endocrine Society in the USA recommends the routine measurement of serum testosterone levels in patients with type 2 diabetes because of the high prevalence.[6,14] Certainly, from our data and the high prevalence in our patient population, the routine screening of all type 2 diabetic men aged 50 years and older in a setting similar to ours would appear to be advisable at first glance.

This approach would lead to another dilemma, regarding how to manage the men now diagnosed with hypogonadism. It is not known whether or not testosterone therapy for hypogonadal men ameliorates their diabetes mellitus. The decision to treat older men, especially with low testosterone levels, or men with chronic diseases associated with low testosterone levels, remains controversial.[9,23,24]

Multiple studies have shown that low testosterone levels are associated with an increase in all-cause mortality that is independent of the metabolic syndrome and diabetes, even after adjusting for confounders.[3,6,25] Cardiovascular events and death can be 2–3 times elevated.[11,23] In contrast, a high endogenous serum testosterone level predicted a reduced five-year risk of cardiovascular events in elderly males in the Osteoporotic Fractures in Men (MrOS) study.[24] It is uncertain whether or not testosterone replacement reverses the detrimental effects of a low testosterone level.

It was demonstrated in the Testosterone Replacement in Hypogonadal Men With Type 2 Diabetes and/or Metabolic Syndrome (TIMES2) study on hypogonadal men with type 2 diabetes or metabolic syndrome that transdermal testosterone replacement had beneficial effects on insulin resistance, total and LDL cholesterol, lipoprotein(a), body composition, libido and sexual function.[26] Any benefit on glucose metabolism or visceral adiposity in obese men with type 2 diabetes could not be demonstrated in another recent trial.[27]

Wang et al. summarised the results of several trials that evaluated the metabolic effect of testosterone replacement.[3] Total cholesterol, and also LDL cholesterol in some studies, showed a small but significant fall. High-density lipoprotein can increase, decrease, or remain unchanged. TGs do not change, but lipoprotein(a) falls significantly after therapy. It also has beneficial effects on body composition and on bone.

Some trial data suggest that patients with low testosterone levels who receive testosterone replacement have a significantly better chance of survival than those who are not treated.[6,19,23,28] Unfortunately, recent trial data demonstrated that the use of testosterone was associated with an increased risk of adverse outcomes, such as a stroke, myocardial infarction and death.[29–32] This will need to be confirmed in larger trials. Not many large trials have evaluated the longterm potential risks, such as prostate cancer and cardiovascular events.[6,28,32–34]

In conclusion, this study confirmed the high prevalence of low testosterone levels in diabetic male patients in a tertiary setting. The associations of low testosterone levels were identified. However, universal testing remains controversial owing to uncertainty about the beneficial and detrimental effects of testosterone therapy in this population group. The ADAM questionnaire was not useful in identifying subjects with a low testosterone level.

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