

The prevalence and associations of erectile dysfunction in a South African male diabetic urban population

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Background: Erectile dysfunction (ED) is a common condition in patients with type 1 or type 2 diabetes mellitus. The prevalence and predictors in our patient population are unknown since minimal data exist for this condition in South Africa.

Method: An observational, cross-sectional study was performed on 150 consecutive male patients aged ≥ 50 years, with either type 1 or type 2 diabetes mellitus, attending the Steve Biko Academic Hospital Diabetes Clinic. These patients were evaluated for diabetes mellitus control and medical complications, and for the presence of ED. Morning serum testosterone levels were determined.

Results: Some degree of ED was reported in 95% of the patients, with 51% reporting serious dysfunction. Using multivariate logistic regression, it was determined that the significant factors associated with ED were age, body mass index, the peripheral neuropathy score and diuretic therapy. Differences in quality-of-life scores were seen in some ED subgroups.

Conclusion: This study confirms the high prevalence of ED in diabetic male patients in a tertiary setting. It is suggested that universal screening should be performed for this population group. Multiple predictors of ED were identified in this study. ED negatively affected quality of life, but not in a statistically significant way.

Keywords: cardiovascular disease, diabetes mellitus, diuretic therapy, erectile dysfunction, glycaemic control, peripheral neuropathy

Introduction

Erectile dysfunction (ED) is a common problem in men with type 1 or type 2 diabetes mellitus, but it is often missed by treating physicians.^{1–3} It occurs at a younger age and with greater frequency in men with diabetes mellitus compared to non-diabetic men.^{1–3} The prevalence of erectile dysfunction in the general adult population in the USA was found to be between 18% and 31%, with up to 78% of men ≥ 75 years being affected.^{4,5}

A prevalence of 35% ED was found in a study as early as 1980 in patients with diabetes mellitus.¹ The prevalence of ED was found to be 49% in men aged 40–88 years in a Canadian study,⁶ while severe ED was found in 30% of men in a large study in Israel.⁷ A prevalence of ED of as high as 71% was also demonstrated in another study in France.³

In South Africa, minimal data exist in this regard. De Klerk et al. reported a prevalence of 77% of ED in users of primary care in a black and mixed race urban population in the Western Cape.⁸ Diabetes mellitus was one of the significant associated diseases, with a crude odds ratio of 3.35 (p 0.001). Webb and Rheeder found some degree of ED in 88% of men with type 1 or type 2 diabetes mellitus screened for complications at primary healthcare clinics in Tshwane.⁹ Thirty-six per cent of these patients had severe ED.⁹

Multiple modifiable risk factors were found to be independently associated with ED in several trials, including diabetes mellitus, obesity, current smoking and hypertension.^{5,6} The prevalence of ED increased progressively with age. Other important associations were treatment with insulin or oral hypoglycaemic agents, retinopathy, and symptomatic autonomic and peripheral neuropathy.¹ The duration of diabetes mellitus, the presence of ischaemic heart disease, nephropathy and poor glycaemic control may also be associated with ED.¹

Men with ED are also more likely to have hypertension and diabetes mellitus, or to have undiagnosed hyperglycaemia.^{6,10} ED severity seems to increase with age, diabetes mellitus duration, poor glycaemic control, the presence of microvascular complications, diuretic therapy and cardiovascular disease.⁷ The consumption of small amounts of alcohol and physical activity might be protective.

ED is often related to organic causes, such as vasculogenic and neurological abnormalities.^{3,11} The medical therapy on which these patients are placed can also contribute to ED.⁷ An underlying cause is often found after extensive evaluation in patients with ED, including conditions such as hypogonadism.^{12–14} Owing to insufficient evidence, it is unclear whether routine hormonal blood tests, such as the determination of serum testosterone levels, should be undertaken in all patients with ED.^{15,16}

ED and atherosclerosis share similar risk factors, such as smoking, diabetes mellitus, dyslipidaemia, hypertension and obesity. There seems to be a strong link between ED and atherosclerotic vascular disease.^{6,10,17,18} Endothelial dysfunction is the common underlying factor linking ED with cardiovascular disease.^{19–21} This plays an important role in the development of atherosclerosis and systemic vascular diseases, such as diabetes mellitus, hypertension, dyslipidaemia, ischaemic heart disease, strokes and claudication.²⁰

The symptoms of ED probably precede cardiovascular events.^{21,22} ED can be an early marker for atherosclerosis, cardiovascular risk and subclinical vascular pathology.^{17,19,20,23} It can also be predictive of the presence and extent of subclinical atherosclerosis, independent of traditional risk factors.²¹ The overall ED prevalence in men with coronary artery disease seems to be high.^{17,22} ED prevalence in acute coronary syndrome was found to differ

according to the extent of coronary artery disease, with a higher prevalence in patients with worse atherosclerosis. Coronary atherosclerosis seems to be more severe in patients with ED.^{17,23} It has also been demonstrated in several prospective studies that ED can be predictive of coronary heart disease, cardiovascular events and death in patients with diabetes mellitus specifically.^{7,8,24}

Since it has been suggested that ED might be an early symptom of generalised cardiovascular disease, patients should probably be systematically screened for ED as part of periodic examination programmes.^{23,25,26} This could lead to early detection and treatment of modifiable vascular risk factors, or existing vascular disease.^{22,25,26}

Men with diabetes mellitus who develop ED experience a significant decline in quality of life, and an increase in depressive symptoms.^{2,27} Depression is also an important factor in the development of ED in patients with diabetes mellitus. The prognosis for ED in men with diabetes mellitus is poor. It was found that only 9% of these men regained erectile function over a five-year period in one prospective study. The development of ED was also significantly associated with poor glycaemic control and the appearance of neuropathic symptoms in the intervening five years.²⁸

Method

Setting

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

Subject selection

One hundred and fifty consecutive convenience sampled male patients aged ≥ 50 years, with either type 1 or type 2 diabetes mellitus, were included. This study formed part of a larger study on late-onset hypogonadism, so men aged < 50 years were not included.

Research procedures

Information was obtained from the patients themselves, their hospital and clinic files, the hospital laboratory system, and from questionnaires which the patients completed.

Demographic variables, such as age, race, smoking history and employment status pertaining to the patients were recorded.

Clinical variables, including the type of diabetes mellitus, as well as the presence of hypertension and time since diagnosis, were recorded. A previous history of stroke, myocardial infarction, amputation, foot ulcerations, cataracts, revascularisation, nephropathy or retinopathy requiring laser therapy was obtained. Blood pressure was taken, body mass index (BMI) was calculated, and waist circumference (WC) measured. The medications used by patients at the time of the study were recorded.

The Sexual Health Inventory for Men (SHIM) questionnaire was completed by the patients.²⁹ This is a basic five-point questionnaire on ED. Each answer is graded from 0 (no sexual activity or attempt at intercourse) to 5 (very good sexual function). The maximum score that patients could obtain was 25 and the minimum was 1. Based on the SHIM questionnaire, the patients were divided into groups:

- *Severe ED (grade 4):* 1–7.
- *Moderate ED (grade 3):* 8–11.

- *Mild to moderate ED (grade 2):* 12–16.
- *Mild ED (grade 1):* 17–21.
- *No ED (grade 0):* ≥ 22 .

This questionnaire was completed by the study participants, with assistance from a trained medical professional, where needed.

A basic health-related, quality-of-life questionnaire, i.e. the EuroQol (EQ-5D) health questionnaire, was completed by the patients.³⁰ This questionnaire evaluates five different aspects, namely mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Patients scored 0 if they had no impairment, 1 if they had moderate problems, and 2 if they had severe impairment, adding up to a maximum of 10 points.

The World Health Organisation Rose angina questionnaire was used to diagnose intermittent claudication.³¹ It consists of nine questions, and based on the patients' choice (out of two possible answers), intermittent claudication was either diagnosed or ruled out. A peripheral neuropathy questionnaire, i.e. the modified Neuropathy Symptom Score, was also completed.³² This questionnaire contains five questions on the symptoms of peripheral neuropathy. Patients could answer "no" or "yes", and grade the peripheral neuropathy by answering "worse at night".

All four questionnaires were chosen for their simplicity and brevity. Although none of them were validated in a South African population, they have been used and validated in other international institutions.

Laboratory measurements

Biochemical variables included routine tests, such as a serum creatinine, serum low-density lipoprotein (LDL) cholesterol and the haemoglobin A_{1c} (HbA_{1c}) value. After the exclusion of a possible urinary tract infection with a spot urine dipstick, a spot urine specimen was collected to measure the albumin to creatinine ratio. Total testosterone was the only non-routine test that was performed.

Fasting blood tests were carried out between 7h00 and 10h00 and were immediately refrigerated. They were transported to the Dr WJH Vermaak laboratory for analysis on the same day. The laboratory-specific normal reference range at this laboratory for total testosterone in males aged ≥ 50 years is 9.9–27.8 nmol/l.

Data analysis

Data were analysed with Stata[®] 12.³³ 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. To determine which variables to use in the multivariate model, univariate logistic regression was performed to evaluate the relationship between demographic, clinical and biochemical variables, and the different health-related questionnaires.

Variables with a p -value < 0.250 were entered into a multivariate model, with manual backward elimination based on the p -values in the model. Non-significant variables were dropped based on the p -value. Sensitivity, specificity, positive and negative predictive values were calculated. To determine the calibration of the final model, receiver operating characteristic (ROC) curve analysis was performed with calculation of the c-statistic. Tenfold cross-validation of the area under the ROC curve was used for validation.

Table 1: The baseline characteristics of the study patients (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 medical complications			
Hypertension	142 (94.7)		
Past or present cardiovascular disease*	61 (40.7)		
Proliferative diabetic retinopathy	38 (25.3)		
Peripheral neuropathy	64 (43.2)		
Intermittent claudication	10 (6.7)		
Present or past cataracts	86 (58.5)		
Microalbuminuria	72 (48.0)		
Other			
Age		62 (7.9)	
Diabetes mellitus duration (years)		15 (8.7)	
Hypertension	142 (94.7)		
Hypertension duration (years)			12 (7–22)
Systolic blood pressure (mmHg)		134 (15.5)	
Diastolic blood pressure (mmHg)		77 (9.3)	
Current smoker	24 (16.0)		
Past smoker	42 (28.0)		
Body mass index (kg/m ²)		30.7 (5.37)	
Waist circumference (cm)		112 (16.4)	
Medications			
On insulin	127 (84.7)		
On metformin	96 (64.0)		
On statin	140 (93.3)		
On diuretics	123 (82.0)		
On fibrates	22 (14.7)		
On beta blockers	68 (45.3)		
Laboratory tests			
Serum creatinine (µmol/l)			96 (79–133)
HbA _{1c} (%)			7.9 (6.8–9.3)
Serum total testosterone (nmol/l)			9.88 (7.04–14.13)
Low total testosterone (nmol/l)	75 (50.0)		
Total cholesterol (mmol/l)		4.09 (0.97)	
TGs (mmol/l)			1.90 (1.20–2.50)
HDL (mmol/l)		0.99 (0.32)	
LDL (mmol/l)		2.33 (0.70)	

Note: HbA_{1c}: haemoglobin A_{1c}; HDL: high-density lipoprotein, IQR: interquartile range, LDL: low-density lipoprotein, SD: standard deviation, TGs: triglycerides
 *:Cardiovascular disease defined as any of the following: previous myocardial infarction; typical angina; ECG evidence of past myocardial infarction; angiographic or MIBI or stress ECG evidence of ischaemic heart disease

** :SD = Standard deviation

***:IQR = Interquartile range

Table 2: The prevalence of erectile dysfunction

Erectile dysfunction (grades)*	n (%)
Grade 0	7 (4.7)
Grade 1	17 (11.3)
Grade 2	28 (18.7)
Grade 3	21 (14.0)
Grade 4	77 (51.3)
Total	150 (100.0)

*According to the Sexual Health Inventory for Men questionnaire, a total score of 22–25 meant no erectile dysfunction (grade 0); 17–21, mild erectile dysfunction (grade 1); 12–16, mild to moderate erectile dysfunction (grade 2); 8–11, moderate erectile dysfunction (grade 3); and 1–7, severe erectile dysfunction (grade 4)

Results

Ninety-one per cent of the patients had type 2 diabetes mellitus. The mean age was 62 years [standard deviation (SD) 7.9]. Just over half of the patients were white (53%) and 30% were black. The mean duration of diabetes mellitus was 15 years (SD 8.7). Ninety-five per cent of the patients were previously diagnosed with hypertension, but this was relatively well controlled, with a mean systolic blood pressure (SBP) of 134 mmHg (SD 15.5) and mean diastolic blood pressure of 77 mmHg (SD 9.3). The patients were obese, with a mean BMI of 30.7 kg/m² (SD 5.4), and a mean WC of 112 cm (SD 16.4). Sixty-six per cent of the patients were current (24%) or past (42%) smokers.

The median serum creatinine was 96 µmol/l [interquartile range (IQR) 79–133]. The patients' diabetes mellitus was better controlled

Table 3: Total testosterone in the different erectile dysfunction categories

Erectile dysfunction	Normal total testosterone*		Low total testosterone**		Total (%)	
	n	(%)	n	(%)	n	(%)
Grade 0	3	(42.7)	4	(57.1)	7	(100.0)
Grade 1	11	(64.7)	6	(35.3)	17	(100.0)
Grade 2	10	(35.7)	18	(64.3)	28	(100.0)
Grade 3	12	(57.1)	9	(42.9)	21	(100.0)
Grade 4	39	(50.7)	38	(49.4)	77	(100.0)
Total	75	(50.0)	75	(50.0)	150	(100.0)

*Normal total testosterone: 9.9–27.8 nmol/l

**Low total testosterone: < 9.9 nmol/l

Table 4: Summary of univariate analysis of multiple statistically significant variables with erectile dysfunction (grade 0–2 versus grade 3–4 erectile dysfunction)

Variable	ED grades 0–2	ED grades 3–4	p-value
Age [mean (SD)]	59 (6.6)	64 (8.0)	< 0.001
Race			
White, n (%)	21 (40.4)	58 (59.2)	
Black, n (%)	16 (30.8)	29 (29.6)	
Coloured, n (%)	8 (15.4)	7 (7.1)	0.033
Asian, n (%)	7 (13.5)	4 (4.1)	
Smoker			
Never, n (%)	30 (57.7)	54 (55.1)	
Current, n (%)	13 (25)	11 (11.2)	0.026
Past, n (%)	9 (17.3)	33 (33.7)	
Systolic blood pressure [mean (SD)]	130 (14.7)	136 (15.6)	0.034
Body mass index [mean (SD)]	29 (5.0)	31.6 (5.4)	0.006
Waist circumference [mean (SD)]	108 (15.7)	115 (16.4)	0.021
Serum creatinine [median (IQR)]	85 (76–106)	99 (83–146)	0.008
Peripheral neuropathy score [mean (SD)]	1.9 (2.2)	3.3 (3.0)	0.005
On a diuretic, n (%)	33 (63.5)	90 (91.8)	< 0.001

Note: ED: erectile dysfunction, IQR: interquartile range, SD: standard deviation

Table 5: Multivariate associations for erectile dysfunction (grades 0–2 versus grades 3–4)

Associations	OR	SE	95% CI (lower limit)	95% CI (upper limit)	p-value
Age	1.11	0.03	1.05	1.17	< 0.001
Body mass index	1.09	0.05	1.00	1.18	0.050
Peripheral neuropathy score	1.22	0.10	1.04	1.45	0.018
On diuretics	5.26	2.75	1.89	14.68	0.002

Note: CI: confidence interval, OR: odds ratio, SE: standard error

Table 6: 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
ED	Before	0.770	0.041	0.690	0.850
	After	0.720	0.045	0.632	0.807

Note: CI: confidence interval, ED: erectile dysfunction, ROC: receiver operating characteristic SE: standard error

Table 7: Erectile dysfunction and quality-of-life score (EQ-5D)

Erectile dysfunction category	n	Quality-of-life score		
		Median*	Interquartile range	
			25th Percentile	75th Percentile
Grades 0–1	24	1	0	2
Grades 2–3	49	1	0	3
Grade 4	77	2	0	3

Note: EQ-5D: EuroQoL

*Kruskal-Wallis test: $p < 0.0513$

than expected, with a median HbA_{1c} of 7.9% (IQR 6.8–9.3). The mean LDL was above target at 2.33 mmol/l (SD 0.7). The median triglycerides was 1.90 mmol/l (IQR 1.20–2.50). The median serum total testosterone was 9.88 nmol/l (IQR 7.04–14.13).

The baseline characteristics of patients' therapy and their diabetic complications are shown in Table 1. Forty-one per cent of patients were known to have cardiovascular disease, and less than 7% had intermittent claudication, as defined by the Rose questionnaire. Microvascular complications were common. Symptoms of significant peripheral neuropathy were present in 43% of the study population, microalbuminuria in 48% of patients, and proliferative diabetic retinopathy in 25%. Fifty-nine per cent of the study participants had cataracts at some point.

Eighty-five per cent of the patients had to be managed on insulin therapy. Metformin was prescribed to 64% of them. Statin usage was high at 93%, but fibrate use was low at 15%. Diuretics were prescribed to 82% of the study population, and 45% of the patients were on beta blockers.

The prevalence of erectile dysfunction

The prevalence of ED is shown in Table 2. Less than 5% of patients had no ED (grade 0), and 51% of patients had severe ED (grade 4). Forty-four per cent had milder degrees of ED.

Total testosterone levels in patients with erectile dysfunction

The distribution of low and normal total testosterone in the different ED categories is demonstrated in Table 3. The Fisher's exact result of 0.369 was non-significant ($p > 0.05$), which implied that there was no association in this study between the two variables of total testosterone and ED.

Associations of erectile dysfunction

The statistically significant univariate associations of ED are summarised in Table 4. These variables were age, race, smoking status, SBP, BMI, WC, serum creatinine, the peripheral neuropathy score and diuretic usage. To simplify the statistical analysis, and because of the low numbers in some of the ED categories, ED was regrouped into two groups, i.e. grades 0–2 and grades 3–4, and then compared.

Age, BMI, the peripheral neuropathy score and diuretic therapy were significant multivariate associations of ED (grades 0–2 versus grades 3–4) (Table 5).

The area under the ROC curve was 0.797 for this model in predicting ED. The sensitivity was 90%, the specificity was 55%, the positive predictive value was 80%, the negative predictive value was 73%, and 78% was correctly classified. Table 6 summarises the the tenfold cross-validation of the area under the ROC curve.

Erectile dysfunction and quality of life

When ED was regrouped into three categories to ensure adequate numbers in each group, i.e. grades 0–1, grades 2–3, or grade 4, an association was demonstrated with quality of life, especially between the grades 0–1 and grade 4 ED groups. This test approached, but did not reach, statistical significance. (Table 7)

Although the EQ-5D has not been validated in a South African population, the Cronbach's alpha reliability coefficient internal consistency was 0.7610, which meant that it was acceptable to use in our setting.

Discussion

ED was found in 95% of this group of patients with type 1 and type 2 diabetes mellitus. Fifty-one per cent reported serious ED. The prevalence in our study was higher than that described in the literature.^{1,3,4,6–9} This may be because of patients' advanced medical complications, co-morbid diseases and numerous drug therapies.^{34,35} There was also an exceptionally high number of current or ex-smokers (44%) in our patient population. The higher prevalence in this study could also be explained by the exclusion of younger patients with diabetes mellitus, compared to other studies.^{1–3}

Univariate associations were age, race, smoking status, SBP, BMI, WC, serum creatinine, the peripheral neuropathy score and diuretic therapy. After multivariate logistic regression, remaining significant factors were age, BMI, the peripheral neuropathy score and diuretic therapy. Statistically significant associations with ED were not demonstrated with other drug classes, such as beta

blockers and fibrates. Predictors of ED were very similar to those reported in the literature.^{1,5–7,10}

Using these variables in a model to predict ED, the area under the ROC curve was 0.797, which implied good discrimination. This model performed well on most of the statistical measures. Although the specificity was poor at 55%, the sensitivity was 90%, which means that this model could be used for screening for this condition. Seventy-eight per cent of cases were correctly classified.

Distinct and independent sets of observations are used in cross-validation to estimate the model and to evaluate prediction error. The estimate of the area under the ROC curve for the aforementioned model was larger than the cross-validated estimate. However, the difference was relatively small, suggesting the absence of over-fitting in the logistic model for ED. It could be expected that the area under the ROC curve would probably not be much higher than 0.80 in a new group of patients.

The testosterone levels did not differ significantly between the different ED groups. The different ED subgroups differed regarding quality of life, and this nearly reached statistical significance. This difference in quality of life was especially demonstrated between the grades 0–1 and grade 4 ED groups. Poorer quality of life was experienced by the latter group. ED's negative effect on quality of life has been described in the literature.²

There were several limitations to this study. It was conducted in a tertiary outpatient diabetes mellitus clinic, where most of the patients had medical complications and numerous co-morbid conditions. Therefore, the results cannot be generalised to the majority of diabetes mellitus patients who follow-up at primary healthcare facilities. The number of patients with type 1 diabetes mellitus is small, and should probably be studied separately. The pathogenesis may be different, with some overlapping factors.

By enrolling 150 consecutive patients in the study, selection bias was to some degree minimised, but not entirely eliminated. A limited number of Asian and mixed ancestry 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 outside corroboration, such as a history of ischaemic heart disease. Owing to the use of multiple examiners with different levels of expertise, only proliferative diabetic retinopathy (either objectively observed, documented in the ophthalmology notes, or based on a history of laser therapy or haemorrhage by the patients) was reported.

Performing a repeat confirmatory testosterone level test, a serum albumin test to calculate the bioavailable testosterone, or a serum luteinising hormone (LH) test to distinguish primary from secondary hypogonadism was not possible because of funding issues. Patients with low testosterone levels were referred to their relevant doctor for further workup, which would have included a serum LH level test, and further relevant investigations, dependent on that result. The questionnaires were also selected for their simplicity and brevity, not necessarily because of superior accuracy, owing to time constraints.

ED is associated with cardiovascular disease, as described in the literature.^{6,10,17,18} It is uncertain how many of the patients in our study with ED had subclinical cardiovascular disease, and if they should have been screened for cardiovascular disease.

Testosterone therapy may be useful for improving vasculogenic ED in men with low or low to normal testosterone levels, especially with serum testosterone levels below 12 nmol/L.³⁶ It can moderately improve the number of nocturnal erections, sexual thoughts, number of occasions of successful intercourse and erectile function, but it has no effect on erectile function in eugonadal men.³⁶ This effect tends to decline over time, and the risks and benefits, as well as long-term safety data, are not available, especially regarding prostatic disease and cardiovascular health.^{36,37}

While effective therapies are not available in the South African public health sector, the prevention of ED is important. A period of intensive glycaemic therapy significantly reduced the prevalence of ED 10 years later in men with type 1 diabetes mellitus who had some target organ damage at baseline in the Diabetes Control and Complications Trial.³⁸ The risk of ED was directly associated with mean HbA_{1c} during the trial duration.

Conclusion

This study confirmed the high prevalence of ED in a tertiary diabetic clinic setting, and that it may negatively affect quality of life. The high prevalence of ED should prompt all male patients aged ≥ 50 years with diabetes mellitus to be screened at tertiary clinics for this condition. Moreover, the clear association that is well described in the literature between ED and cardiovascular disease should prompt the screening of patients with ED for ischaemic heart disease.

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