Journal of Endocrinology, Metabolism and Diabetes of South Africa 2022; 27(2):78–82
https://doi.org/10.1080/16089677.2022.2031464

JEMDSA
ISSN 1608-9677 EISSN 2220-1009

ARTICLE

Total testosterone level may have no influence on the occurrence and severity of erectile dysfunction in males aged between 30 and 60 years living with type 2 diabetes

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Background: Erectile dysfunction is the most common sexual disorder in type 2 diabetes. Its pathogenesis may involve various disturbances including endothelial dysfunction and dysautonomia. The involvement of a low testosterone level is still debated. The aim of this study was to evaluate the contribution of total testosterone during erectile dysfunction in patients living with type 2 diabetes.
Method: A cross-sectional study was conducted in a population of male with type 2 diabetes, aged 30–60 years, and enrolled at the National Obesity Centre of the Yaoundé Central Hospital. Non-diabetic conditions that could affect testosterone level were excluded. Erectile dysfunction was assessed using the IIEF-5 questionnaire. Total testosterone was measured by ELISA. The relationship between erectile dysfunction and total testosterone has been explored through correlation using Pearson's coefficient. The significance threshold was set at 0.05.
Results: A total of 83 participants were included, with an average age of 47.9 ± 7.8 years. The median duration of diabetes was 24 (5; 72) months. The frequency of ED was 65.1%, severe for 50% of cases and significantly associated with the duration of diabetes (OR = 7.5 [2.4; 22.8]). The mean testosterone level was 14.3 ± 5.1 nmol/l. A low level of testosterone was found in 8.4% (7/83) of participants, and sedentary lifestyle was significantly associated with low testosterone level (OR = 4.1 [1; 15.4]). There was no difference between the mean total testosterone level of patients with ED (14.1 ± 4.7 nmol/l) and those without (14.3 ± 5.9 nmol/l) ($p = 0.8$). No association was found between total testosterone level and IIEF-5 score ($r = -0.05$; $p = 0.5$).
Conclusion: Erectile dysfunction occurs in two out of three people living with type 2 diabetes and is severe for half of the cases. Total testosterone level does not seem to have an influence on the onset or severity of ED in male under 60 years with type 2 diabetes, but it is associated with a sedentary lifestyle.

Keywords: erectile dysfunction, total testosterone level, type 2 diabetes

Background

Erectile dysfunction (ED) is defined as the permanent and recurrent inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse.[1] It is a widespread condition worldwide and its prevalence varies from one population to another. In the United States, the Massachusetts Male Aging Study (MMAS) found a 52% prevalence of ED in men aged 40–70 years.[2] It is an under-diagnosed condition because, as it is still considered a 'taboo' subject, patients tend not to bring it up spontaneously in front of their doctor.[3] Diao *et al*. in Senegal and Oyelade *et al*. in Nigeria have reported community prevalences of 26% and 58.9% respectively.[4,5] An essential aspect of the condition is that it alters the quality of life of men who suffer from it, leading to often invisible psychological distress in the form of marital conflict, low self-esteem and a sense of failure as a man.[6] The mechanisms contributing to ED in diabetes are multiple, including autonomic neuropathy, endothelial dysfunction and sometime iatrogenic causation by multiple medications and psychological disorders such as mental depression, which is not rare in type 2 diabetes (T2DM) patients.[7]

In fact, ED affects one in two patients with diabetes, which is four times higher than that of the general population.[8] Most recent studies in Africa show prevalence rates of 50%.[9,10] The number of people living with T2DM and diagnosed with ED increases significantly with duration of T2DM, age, poor glycaemic control, and is correlated with the occurrence of chronic complications of T2DM, particularly cardiovascular, renal and neurological complications.[11] A low testosterone level is classically recognised as a physiological mechanism of ED occurring with age in patients without diabetes. It was found in 20% of T2DM patients below the age of 60 by Kapoor *et al*., highlighting its possible contribution to the pathogenesis of ED.[12] However, its involvement is still debated and subject to controversy. The aim of this study was to evaluate the contribution of testosterone level in a population of Cameroonian patients living with T2DM and ED.

Methods

Study design and setting

We carried out a cross-sectional study at the National Obesity Center of the Yaoundé Central Hospital (HCY). This is a tertiary and referral hospital in the urban city of Yaoundé. There are several specialised services, including the Endocrinology Department and the National Obesity Centre, from which we recruited participants. Our study ran from November 2019 to June 2020.

Participants

We included adult males aged between 30 and 60 years, living with type 2 diabetes on an outpatient basis. We excluded from the study participants with known abnormalities in sexual differentiation; with a known history of a condition that may cause erectile dysfunction such as chronic kidney disease, dysthyroidism, chronic liver disease; or who had undergone genitourinary tract surgery, or follow-up for prostate pathology.

We also excluded participants who were taking a drug that may promote erectile dysfunction such as beta-blockers, spironolactone and psychotropic drugs at the time of the study, and those already receiving treatment for a previous diagnosis of erectile dysfunction. We also excluded participants with a glomerular filtration rate of less than 30 ml/minute, and/or an alanine amino transferase value greater than three times normal.

Sample size estimation

We used the sample size formula for a difference in mean between groups, described in the Withley and Ball manual.[13] Our hypothesis was a 20% difference in total testosterone between patients with T2D and ED and those without. Given the mean total testosterone level of patient with T2D without erectile dysfunction incoming from Mushtaq et al. of 21.6 ± 3.9 nmol/l[14] and an estimated 20% difference in total testosterone, an estimated sample size of 22 participants for each group (with and without ED) was calculated using Whitley and Ball (2002).[13] We proceeded by a consecutive sampling.

Data assessment

We used a data collection form to collect data on age, professional and marital status, history of diabetes (month and year of diagnosis, regularity of consultations, chronic complications of diabetes, current treatment, and glycated haemoglobin less than six months old); relevant history (hypertension, hyperthyroidism, chronic at-risk consumption of tobacco and/or alcohol, HIV infection, chronic viral hepatitis).

We evaluated erectile dysfunction using the IIEF-5 questionnaire (five-item version of the International Index of Erectile Function). Thisis a five-item self-administered questionnaire with answers rated from zero to five. It evaluates sexual function over a period of at least six months and takes into account sexual desire (question 1), erection (questions 2, 3 and 4) and sexual satisfaction (question 5). It is rated from 1 to 25; the participant had erectile dysfunction if the score varied between 5 and 20. In general we considered the scores to show severe erectile dysfunction (5–10); moderate (11–15); mild (16–20); normal result (21–25); non-interpretable result (1–4). Participants with uninterpretable results were excluded. The questionnaire was self-administered by each participant. Blood pressure, abdominal circumference and determined body mass index using weight and height were measured.

All blood samples were collected in the morning between 8 and 10 am respecting the circadian rhythm of testosterone secretion and after a fasting period of at least 6 hours. The last meal was ingested at 8 pm the day prior to blood sample collection. Then, we determined the testosterone level in the blood samples using the competitive enzyme-linked immunosorbent assay.

Serum creatinine was determined and estimated glomerular filtration rate was calculated using the MDRD formula.

Operational terms

A low testosterone level was defined according to the Endocrine Society of Clinical Practice Guideline criteria, by a serum total testosterone (TT) value less than or equal to 8 nmol/l. Values above 12 nmol/l are considered normal; those between 8 and 12 nmol/l are considered borderline testosterone levels.[12] Male hypogonadism was defined as the presence in men of symptoms/signs of androgen deficiency such as ED, combined with biochemical evidence of this deficiency. It is said to be straightforward for a testosterone level ≤ 8 nmol/l with or without ED, and borderline for a testosterone between 8 and 12 nmol/l with ED.

Statistical analysis

All the data collected were analysed using the software SPSS (Statistical Package for Social Sciences) version 23.0 (IBM Corp, Armonk, NY, USA). Quantitative variables were expressed in terms of mean and standard deviation (SD) or median with the interquartile range (Q25; Q75), while qualitative variables were expressed as counts and proportions. The comparison of the means of the quantitative variables between two groups was done using Student's *t*-test. Factors associated with ED and testosterone level were determined using Fisher's exact test. The odds ratio (OR) and its 95% confidence interval were used to quantify the degree of association. The relationship between ED (evaluated by the IIEF-5 score) and total testosterone level has been tested through correlation and presented with the Pearson correlation coefficient. The significance threshold was set at 0.05.

Ethical approval

We obtained authorisation from Yaoundé Central Hospital and ethical approval from the Institutional Ethical Review Board of the Faculty of Medicine of Biomedical Sciences of the University of Yaoundé 1 (No. 343/UY1/FMSB/VDRC/DAASR/CSD).

Results

Characteristics of the sample

Overall, 83 participants were recruited. The average age of participants was 47.9 ± 7.8 years, with extremes of 31 and 60 years. Some 73.5% of participants had a sedentary lifestyle and 71.1% regularly drank alcohol. Sixteen participants (19.3%) had hypertension. The median of the duration of diabetes since diagnosis was 24 (5; 72) months. Most participants (77.1%) kept their follow-up appointments regularly. Pharmacological treatments for diabetes included oral antidiabetic drugs in 72.3% of cases, and/or insulin in 37.3% of cases. The mean HbA1c of participants was 7.9 ± 2.1%. Thirty-five participants (42.2%) had strict control (HbA1c < 7%). Chronic complications were found in 17 (20.5%) participants. These were mainly diabetic foot (11 participants). The mean BMI was 26 ± 4.1 kg/m^2. In total, 38 patients were overweight (45.8%). The characteristics of the sample are presented in Table 1.

Table 1: Baseline characteristics of the sample

Variables	Overall ($n = 83$)	Percentages
n (%)	83	100
Mean age, year, (SD)	47.9 (7.8)	
Age, min–max, year	31–60	
Comorbidities:		
Physical inactivity	61	73.5
Alcoholism	59	71.1
Active smoking	24	28.9
High blood pressure	16	19.3
HIV infection	2	2.4
Body mass index:		
Underweight	2	2.4
Normal	33	39.8
Overweight	38	45.8
Obesity	10	12
Abdominal obesity	9	10.8
Diabetes control (HbA1c):		
≤ 7%	35	42.2
7%–8.5%	21	25.3
> 8.5%	27	32.5
Vascular complications:		
Stroke	1	1.2
Diabetic foot	11	13.3
Diabetic retinopathy	7	8.4

Frequency, severity and factors associated with erectile dysfunction

The frequency of ED was 65.1% (54/83). It was severe in 27 (50%), moderate in 19 (35.1%) and mild in 8 (14.8%) participants. Factors associated with ED in the sample included: age above 48 years (OR = 2.7 [1.08; 7]), duration of diabetes of at least 24 months (OR = 7.5 [2.4; 22.8]) and the presence of chronic complications of T2DM (OR = 11.7 [1.4; 94]) (Table 2).

Frequency of low testosterone level and its contribution to erectile dysfunction

The mean testosterone level in the sample was 14.3 ± 5.1 nmol/l. Low testosterone level was found in 8.4% (7/83) of the whole sample. Low testosterone level was present in 3/54 people with ED, and 4/29 people without ED. Hypogonadism was found in 21 (25.3%) participants. Sedentary lifestyle was the only factor associated with low testosterone level (OR = 4.1 [1; 15.4], $p = 0.03$) (Table 3). There was no significant difference between the mean total testosterone levels of patients with ED (14.1 ± 4.7 nmol/l) and those without (14.3 ± 5.9 nmol/l) (Figure 1). Similarly, there was no correlation ($r = 0.03$, $p = 0.7$) between total testosterone levels and the IIEF5 score (Figure 2). Also, there was no correlation ($r = -0.05$, $p = 0.5$) between total testosterone and glycated haemoglobin level (Figure 3).

Discussion

The present study assessed the contribution of testosterone in erectile dysfunction in patients living with T2DM. Testosterone is the main androgen in male responsible for sex differentiation of external genitals. It is also useful in the triggering and maintenance of erectile function. ED in T2DM is generally a consequence of the low level of NO resulting in an endothelial dysfunction in the intracavernous tissues. Efficient treatment of ED could improve patients' quality of life. A low testosterone level could be apparent as a remediable cause of ED and for this reason it should be assessed. We measured total testosterone using the immuno-assay method. Although liquid chromatography coupled with mass spectrometry (LC-MS/MS) is the method recommended by the Endocrine Society for determination of androgens, it is more expensive and labour-intensive so that it cannot be easily applicable for cohort studies. Some authors recommend immunoassay in routine assessment of total testosterone. This method is equal and has a sensibility comparable to LC-MS/MS.[15]

Our results show that ED was present in 54/83 participants (65.1%). Nisahan *et al.* and Cho *et al.* had a prevalence of 62.9% and 65.5%, meaning that ED in T2DM is encountered in one patient in two, arising as a frequent complication in males with T2DM and representing an important issue to be assessed.[16,17] Factors associated with ED in the sample included: age above 48 years (OR = 2.7 [1.08; 7]), duration of diabetes of at least 24 months (OR = 7.5 [2.4; 22.8]) and the presence of chronic complications of T2DM (OR = 11.7 [1.4; 94]). All these factors are generally correlated to poor diabetes control.

There was no statistically significant difference between the mean total testosterone levels of patients with ED (14.1 ± 4.7 nmol/l) and those without ED (14.3 ± 5.9 nmol/l) ($p = 0.3$). This suggests that serum total testosterone levels do not

Table 2: Factors associated with erectile dysfunction in the sample

	Erectile dysfunction					
Variables	Yes ($n = 54$)	No ($n = 29$)	OR [IC 95%]	*p*-value	*p*-value	aOR [95% CI]
Age ≥ 48 years	32 (76.2)	10 (23.8)	2.7 [1.08; 7]	0.04	0.2	1.9 [0.6; 5.4]
HbA1c ≥ 8%	25 (67.6)	12 (32.4)	1.2 [0.4; 3]	0.8	–	–
Duration of diabetes ≥ 24months	33 (86.8)	5 (13.2)	7.5 [2.4; 22.8]	< 0.001	0.005	5.2 [1.6; 16.5]
BMI ≥ 25 kg/m²	28 (58.3)	20 (41.7)	0.4 [0.1; 1.2]	0.1	–	–
Abdominal obesity	7 (77.8)	2 (22.2)	2 [0.3; 10.3]	0.4	–	–
High blood pressure	13 (81.3)	3 (18.8)	2.7 [0.7; 10.5]	0.1	–	–
Complications of diabetes	16 (94.1)	1 (5.9)	11.7 [1.4; 94]	0.004	0.1	5.8 [0.6; 51]
Physical inactivity	42 (68.9)	19 (31.1)	1.8 [0.6; 5]	0.2	–	–
Alcohol consumption	39 (66.1)	20 (33.9)	1.1 [0.4; 3.1]	0.8	–	–
Tobacco consumption	19 (79.2)	5 (20.8)	2.6 [0.8; 7.9]	0.1	–	–
Insulin treatment	21 (67.7)	10 (32.3)	1.2 [0.4; 3]	0.8	–	–

aOR: adjusted Odd Ratio; HbA1c: glycated hemoglobin; BMI: body mass index. Statistical significance: $p < 0.05$

Table 3: Factors associated with a decrease in total testosterone level

Variables	Testosterone level < 12 nmol/l *n* = 27 (32.5%)	Testosterone level ≥ 12 nmol/l *n* = 56 (67.5%)	*p*-value	OR [95% CI]
Age ≥ 48 years	15 (35.7)	27 (64.3)	0.6	1.3 [0.5; 3.3]
Duration diabetes > 24 months	10 (26.3)	28 (73.7)	0.3	0.5 [0.2; 1.5]
BMI ≥ 25kg/m²	15 (31. 3)	33 (68.8)	0.8	0.8 [0.3; 2.2]
Abdominal obesity	5 (55.6)	4 (44.4)	0.1	2.9 [0.7;12]
High blood pressure	2 (12.5)	14 (87.5)	0.07	0.2 [0.05;1.1]
Chronic complications	6 (35.3)	11 (64.7)	0.7	1.1 [0.3; 3.5]
Sedentary lifestyle	24 (39.3)	37 (60.7)	0.03	4.1 [1; 15.4]
Alcohol consumption	16 (27.1)	43 (72.9)	0.1	0.4 [0.1; 1.1]
Tobacco consumption	5 (20.8)	19 (79.2)	0.1	0.4 [0.1; 1.3]
Insulin treatment	10 (32.3)	21 (67.7)	1	0.9 [0.3; 2.5]

BMI: body mass index. Statistical significance: $p < 0.05$

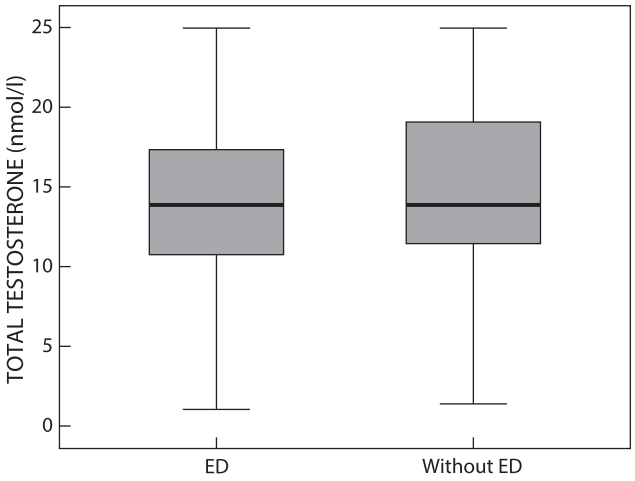

Figure 1: Serum level of total testosterone in patients with and without erectile dysfunction (ED). ED: erectile dysfunction., Total testosterone in patients with ED (red): (14.1 ±4.7nmol/l); without ED (green): (14.3 ± 5.9nmol/l).

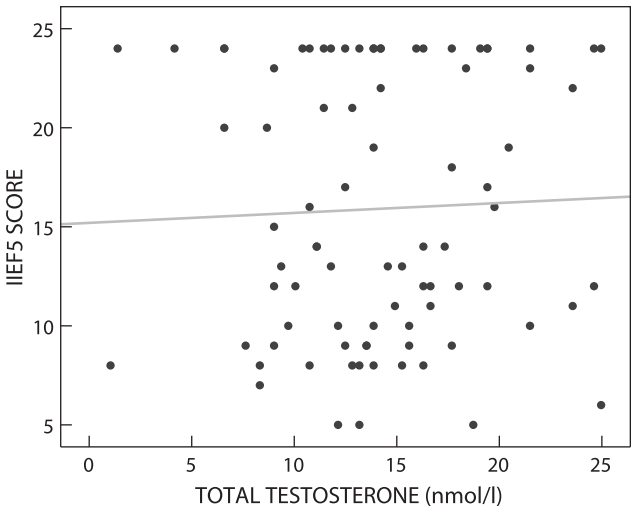

Figure 2: Correlation between total testosterone and severity of ED.

influence the occurrence of ED in T2DM. Kapoor *et al*. found similar results: there were no significant differences in total testosterone levels in men with and without ED (total testosterone

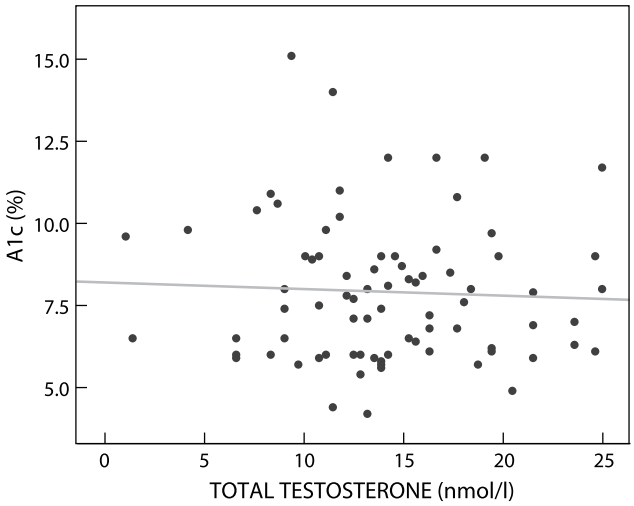

Figure 3: Total testosterone and diabetes control.

12.5 ± 0.09 versus 12.7 ± 0.08 nmol/l, $p = 0.1$).[12] However, a study published in Egypt found that patients with ED had lower total testosterone than those without ED.[18] To justify this disparity of results, the hypothesis put forward would be the concomitant drop in SHBG levels, frequently observed during diabetes, reducing serum transport and therefore testosterone bioavailability. The physiological role of SHBG would be more complex than the simple transport of sex hormones, and would also intervene in the physiopathology of insulin resistance during T2DM. In relation to our results, a meta-analysis concluded that, in the majority of cases, ED in T2DM and its severity are due to neuropathy and vasculopathy and not due to hormonal problems, as confirmed by numerous published studies.[19] Low testosterone level was found only in 8.4% (7/83) of the whole sample. Although testosterone does not influence the occurrence of erectile dysfunction in T2DM patients, sedentary lifestyle was a factor associated with low testosterone level in T2DM with ED (OR = 4.1 [1; 15.4], $p = 0.03$). In fact, there is a relation between BMI and testosterone level. Physical activity improves bioavailability of testosterone by dropping the level of SHBG.

In view of these results, the significance of this study is that health personnel should routinely screen for ED because of its high prevalence. Second, it would be judicious and wise for clinicians to adequately explore all other causes of erectile dysfunction,

which are mainly psychological, neurological and vascular, in diabetic patients before going through testosterone dosage, especially when they practise in the context of low-resource settings, where this examination is expensive for patients who are already under the burden of chronic medication.

Conclusion

Erectile dysfunction is common in patients living with type 2 diabetes, especially as the duration of diabetes goes beyond 24 months. Although a low level of testosterone is rarely found in this population, this hormonal status is associated with a sedentary lifestyle. Total testosterone level did not influence the occurrence and severity of erectile dysfunction in our study.

Abbreviations

BMI (body mass index); ED (erectile dysfunction); T2DM (type 2 diabetes mellitus), IIEF-5 (International Index of Erectile Function 5 item version), ELISA (enzyme-linked immunosorbent assay), SHBG (sex hormone binding globulin).

Disclosure statement – No potential conflict of interest was reported by the authors.

Funding – The authors reported there is no funding associated with the work featured in this article.

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Received: 22-11-2021 Accepted: 17-01-2022