VERSITA

© **2013** ILEX PUBLISHING HOUSE, Bucharest, Roumania
http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **20**(4):401-407
doi: 10.2478/rjdnmd-2013-0040

ANDROGEN DEFICIENCY, ERECTILE DYSFUNCTION AND CHRONIC MICROVASCULAR COMPLICATIONS IN MALE DIABETIC PATIENTS

Olivia Georgescu [1,2,✉], ***Aura Reghină*** [1,2], ***Sorin Ioacără*** [1,2], ***Cătălin Nica*** [2], ***Simona Fica*** [1,2]

[1] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania
[2] Department of Endocrinology, Diabetes and Metabolic Diseases, Elias Emergency University Hospital, Bucharest, Romania

received: October 31, 2013 *accepted*: November 17, 2013
available online: December 15, 2013

Abstract

Background and aim: *Erectile dysfunction (ED) can be present in diabetic patients not only induced by androgen deficiency, but also as a consequence of diabetes chronic complications. The aim of our study was to evaluate androgen status and chronic microvascular complications in patients with diabetes mellitus (DM), with and without ED.* ***Material and methods:*** *292 patients (44 Type 1 diabetes - T1DM/ 248 Type 2 diabetes - T2DM), were evaluated for androgen status: dehydroepiandrosterone (DHEA), free testosterone (FT) and presence of chronic complications. ED was diagnosed by a score under 22 of 5-item International Index of Erectile Function (IIEF). Patients with free-testosterone < 70 pg/ml were considered hypogonadal.* ***Results:*** *Prevalence of ED was higher in T2DM 87.5% than in T1DM 65.9%. In patients with ED the prevalence of hypogonadism was 31.3% in T1DM, 26.7% in T2DM. In older T2DM patients IIEF-score was significantly correlated with DHEA. There was a significant correlation between ED and retinopathy in T1DM, additionally with neuropathy in T2DM.* ***Conclusions:*** *ED is a common comorbidity in diabetic patients, associated with other microvascular complications. Hypogonadal status might explain up to 30% of ED. In older diabetic men, severity of ED is related to lower DHEA.*

key words: *erectile dysfunction, diabetes mellitus, testosterone, chronic complications*

Background and Aims

A worldwide epidemic increase in diabetes mellitus (DM) has occurred in recent decades and will steadily increase in the near future [1]. Erectile dysfunction (ED) is an important cause of decreased quality of life in men with diabetes. ED afflicts more than half of 40-70 years-old males and its prevalence increases with advanced age and duration of diabetes [1]. In diabetic subjects ED occurs earlier than in the non-diabetic population. In many studies its frequency has been reported to be higher in people with DM compared with those without, in part due to autonomic neuropathy and vascular disease [2]. Poor metabolic control and history of diabetic complications (vascular and cardiac events, autonomic or sensory neuropathy, renal disease, retinopathy or diabetic foot) were identified as risk factors for the development of ED [3].

✉ 17 Marasti Avenue, District 1, Bucharest; Postal Code 011461; Tel: 0040724216004; Fax 0040213161614; *corresponding author e-mail*: oliviageorgescu@yahoo.com

Testosterone serum level has an important role in the maintenance of male sexual function, including in the pathogenesis of ED. The age related decrease in men testosterone level is exacerbated by diabetes also [4,5]. Much more, several important studies [6,7] showed low testosterone (total or bioavailable fractions) to be a predictor of type 2 diabetes mellitus (T2DM). Moreover, low sex hormone-binding globulin (SHBG) level (which binds tightly to testosterone and transports it in the circulation) was independently associated with increased risk of diabetes in men [8]. Therefore, ED can be present in male diabetic patients not only induced by androgen deficiency, but also as a consequence of its chronic complications.

The aim of our study was to evaluate the epidemiology of erectile dysfunction (ED), sex hormonal status and chronic microvascular complications in a group of male patients with diabetes mellitus from Bucharest, Romania.

Material and methods

Subject inclusion

The study was approved by the Local Ethics Committee of "Elias" Emergency Hospital, Bucharest. From 500 male patients evaluated in the Endocrinology, Diabetes and Metabolic Diseases Department between January 2009-January 2012, 292 patients gave their written informed consent, according to Helsinki Declaration and were included in the study.

Study subjects were referred to our department for metabolic disturbances. Patients with free testosterone below 70pg/ml were considered hypogonadal. ED was diagnosed based on a score below 22 points on the 5-item validated-standardized questionnaire of International Index of Erectile Function (IIEF) with a structure developed by an International Consensus [9].

Clinical evaluation

We recorded data regarding anthropometrical parameters including height, weight, waist and hip circumference. Weight was measured in light clothing without shoes and height was measured using a stadiometer. Waist and hip circumferences were measured with the patient standing, at the level of umbilicus and pubic symphysis respectively.

Paraclinical evaluation

Diabetic Retinopathy (DR) was diagnosed through direct ophtalmoscopy examination, after pupil dilation and classified as: without DR, background DR, preproliferative DR and proliferative DR [10]. We used the old classification of DR, although present classification is: non-proliferative (mild, moderate, severe) and proliferative.

Chronic kidney disease (CKD) was defined by the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines and the stage of CKD was assigned based on the level of kidney function, according to the KDOQI Classification [11].

Diabetic Neuropathy was diagnosed and staged according to the guidelines for the diagnosis and outpatient management of diabetic peripheral neuropathy [3].

Laboratory evaluation

Blood samples were drawn for biochemical and hormonal tests after a 12 hours overnight fast. We evaluated the metabolic control (glycemia, HbA1c, total cholesterolemia, LDL-cholesterolemia, HDL-cholesterolemia, triglyceridemia) and also data regarding sex hormonal status (total testosterone, sex hormone-binding globulin (SHBG) and dehydroepiandrosterone (DHEA)). The hormonal measurements were performed using an immunochemiluminescent method with Immulite 2000 device. Using the Vermeulen

normogram [12] we estimated the value of free testosterone from total testosterone and SHBG. The normal values were as follow: total testosterone = 181-772 ng/dl, SHBG=32-122 nmol/ l, DHEA 80-560 μg/dl, free testosterone = 58-72 pg/ml.

Table 1. The clinical diagnosis of diabetic peripheral neuropathy.

Stage of neuropathy	Characteristics
0. No neuropathy	No symptoms or signs
1. Clinical neuropathy	
– Chronic painful	Burning, shooting, stabbing pains with or without "pins and needles"; increased at night; absent sensation to several modalities; reduced/absent reflexes
– Acute painful	Severe symptoms as above (hyperesthesiae common), may follow initiation of insulin in poorly controlled diabetes, signs minor or absent
2. Painless with complete/partial sensory loss	Numbness/deadness of feet or no symptoms, painless injury, reduced/absent sensation, reduced thermal sensitivity, absent reflexes
3. Late complications	Foot lesions, neuropathic deformity, nontraumatic amputation

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Software (SPSS) version 17. Data are presented as mean ± standard deviation (SD). Clinical characteristics were compared using the *t* Student Test. The Pearsons coefficients were calculated to evaluate correlations between variables. Significance was defined at *p* value under 0.05.

Results

From the 292 subjects included in the study, 44 were diagnosed with type 1 diabetes mellitus (T1DM) and 248 with type 2 diabetes mellitus (T2DM). Age ranged between 20-75 years (mean age 52.06 ± 3.7 years). The main patients characteristic are presented in Table 2.

Table 2. Characteristics of subjects.

Parameter	T1DM (n=44)	T2DM (n=248)	p
Mean age (years)	32.2±5.3	59±6.7	p=0.0002
Waist (cm)	88.5±4.2	105.1±4.5	p=0.02
Fasting glycemia (mg/dl)	246.7±95.8	198.5±75.6	p=0.002
HbA1c (%)	10.1±2.7	8.8±3.4	NS
Triglyceride (mg/dl)	96.5±16.2	173.9±14.7	p=0.03
HDL-cholesterol (mg/dl)	47.7±6.3	40.8±4.5	NS
BP (%)	25	70	p=0.002
Total testosterone (ng/dl)	419.7±120.3	337.9±97.3	NS
Free testosterone (pg/ml)	76.7±13.4	68.4±9.6	NS
SHBG (nmol/l)	48.1±13.3	38.3±9.6	NS
DHEA-S (μg/dl)	190.5±93.6	140.6±84.7	NS
IIEF-score	18.5±5.8	11.5±4.5	NS

Subjects with T1DM were significantly younger and had a smaller waist circumference. They had worse fasting glycemia, although similar HbA1c compared with those with T2DM. The two groups were similar in terms of sex hormonal status and IIEF score.

The prevalence of ED in the whole study group was 84.24%, higher in T2DM than in T1DM (87.5% vs.65.9%). The incidence of ED increase according to age, from 33.34% in the 20-40 years age group to 87.7% over 60 years.

Prevalence of hypogonadism among patients with ED was 31.37% in subjects with T1DM and 26.73% in those with T2DM. Among hypogonadal patients with T2DM 93.9% have ED, while only 66.6% of T1DM patients have ED (p = 0.04).

A significantly positive correlation between IIEF score and DHEA value was found in T2DM patients over 60 years, while in younger T2DM patients (below 60 years) this correlation was not observed (Figure 1).

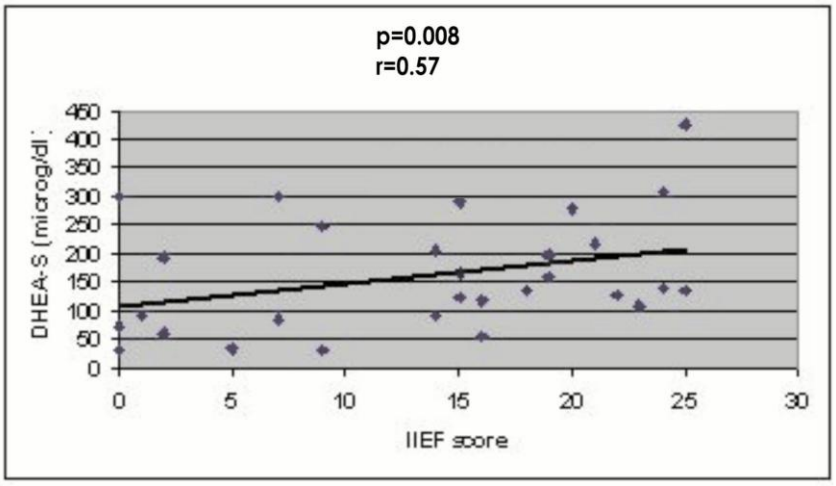

Figure 1. *The higher IIEF-score was associated with higher DHEA value in older men with T2DM.*

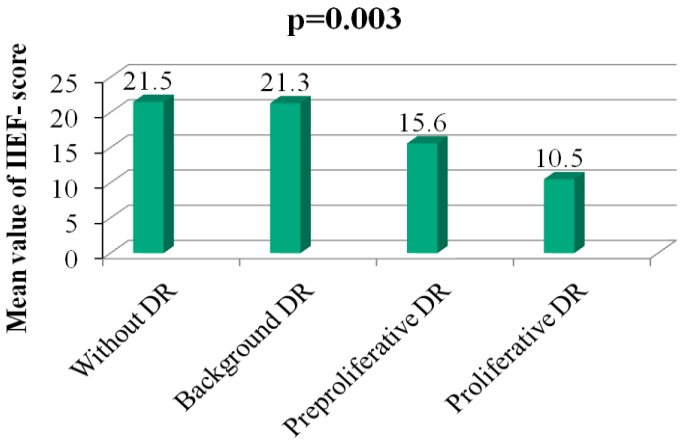

Figure 2. *The correlation between ED and degree of diabetic retinopathy in T1DM.*

Regarding the microvascular complications, we evaluated the association between ED (through IIEF score) and the presence / degree of diabetic retinopathy (DR). Among T1DM subjects, the mean IIEF value was significantly higher in those without DR compared with those with proliferative DR (21.5 vs.10.5 points, p = 0.003), as shown in Figure 2. We couldn't find a significantly difference between IIEF score and the degree of DR, in T2DM.

In our study group, we found 150 patients in different stages of chronic kidney disease (CKD). The prevalence of ED in those subjects was 42% (63 patients). We could not observe a relationship between IIEF score and chronic kidney disease (CKD) in subjects with T1DM. Among T2DM patients, the mean IIEF score was significantly higher in those with stage 1 CKD than in those with stage 3 CKD (20.4 vs.12.73 points, p = 0.03).

Diabetic peripheral neuropathy (DPN) was more frequently diagnosed in T2DM than in T1DM subjects (32.26% vs. 13.64%). After stratification of patients according to the degree of DPN, in patients with T2DM the mean value of IIEF was higher in those without DPN compared to those in stage 3 DPN (20.7 vs.10.5 points, p = 0.04), as shown in Figure 3. For T1DM we could not observe an association between ED and progression of DPN.

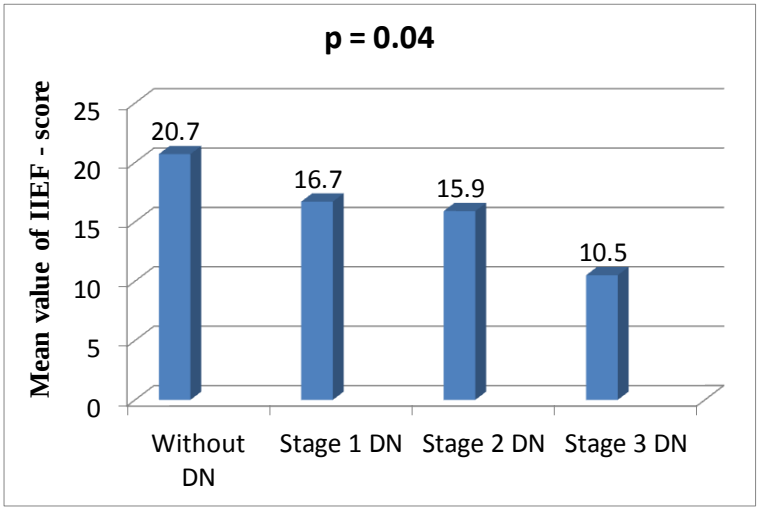

Figure 3. *The correlation between ED and degree of diabetic peripheral neuropathy in T2DM.*

Discussions

The prevalence of ED was higher in our study than in other recent publications [13,14] (84.24% vs. 66-75%). A possible explanation is that the patients who were included in our database were recruited from subjects with DM who were admitted in our department for poor metabolic control. Another explanation could be the different use of the self-reported IIEF questionnaire, the cultural background and the attitude to sexual problems.

Another study conducted in Romania using the Sexual Health Inventory for Men (SHIM) questionnaire in 310 patients with DM aged between 20-78 years showed that 63.2% have ED: 32.95 mild ED, 13.5% moderate and 16.8% severe ED [15].

In our study, the incidence of ED correlated with increasing age, being 2.64 times higher in people over 60 years, compared with the 20 to 40 years age group. This finding is in accordance with data reported by most publications.

Patients with T1DM from our study had lower prevalence of ED and higher mean IIEF score than patients with T2DM. This could be explained by the younger age of subjects in the T1DM group. In fact, the age differences between groups represent a limitation of our study.

According to free testosterone levels, the prevalence of hypogonadism in subjects with ED was higher in our study (29.05%) compared to that reported by other papers (17.6%) [16].

The DHEA value decreases with increasing age. At the age of 60 years, DHEA value decreases to one third of the level attained at the age of 20 years [17]. Therefore, mean DHEA value is negatively correlated with increased age, but also with diabetes duration. In our study, a significant positive correlation between DHEA value and IIEF score was observed, but only for subjects over age 60 years. In a study which enrolled 348 older male patients it was noted that Dehydroepiandrosterone-sulfate (DHEA-S) and also free testosterone values were significantly correlated with IIEF scores. Moreover, treatment

with DHEA improved IIEF score without affecting prostate-specific antigen (PSA), prolactine, total testosterone serum values and also prostate and postmictional volume [18]. Although it remains a controversial hypothesis, it seems that in older males clinical signs and symptoms can be related to the serum changes of DHEA-S and estradiol values [18].

Regarding the association of ED with chronic diabetes complications, it was shown that between 35 and 75% of diabetic patients had ED induced by autonomic neuropathy, ED being more frequent than diabetic nephropathy [13].

Few studies found information regarding the link between ED and diabetic retinopathy (DR) in men with DM. Researchers found that there is an important relationship between ED and DR severity independent of age, diabetes duration, macrovascular comorbidities and cardiovascular risk factors [13]. In our study, we found a statistically significant difference between the severity of ED (expressed by IIEF score) in patients with T1DM without DR compared to those with proliferative DR. A recent analysis including 324 subjects with T2DM found that the presence and severity of DR (but not that of diabetic macular edema) are independently associated with self-reported ED [14].

Sexual dysfunction is common in patients with CKD. This condition has been found to be significantly more common in men with CKD than in the general population. Approximately 50% of male predialysis CKD patients and 80% of male dialysis patients have erectile dysfunction [19]. The frequency of sexual dysfunction increases as renal function deteriorates [20]. In our analysis 42% patients with CKD have ED and its severity expressed by IIEF value is correlated with the stage of CKD in T2DM. The prevalence of ED in CKD subjects is therefore half the prevalence in whole study group, probably because renal impairment in our patients did not exceed third stage of CKD.

Regarding diabetic peripheral neuropathy (DPN), a recent publication [21] that enrolled 90 patients showed that subjects with severe DPN recorded the lowest IIEF score and required the most aggressive treatment. No association between neurophysiological tests and IIEF score was detected. In our analysis, a statistically significant difference regarding the severity of ED (expressed by IIEF score) was observed in T2DM patients between those without clinically DPN and those within the third stage of DPN.

Conclusions

ED is frequent in patients with DM and its incidence is increasing with age. In our study ED was associated with the presence of chronic diabetes complications and its severity correlated with progression of the microvascular complications. Hypogonadal status can explain 30% of ED in both T1DM and T2DM. In older diabetic men, the severity of ED is related to lower DHEA values.

REFERENCES

1. Feldman HA, Goldstein I, Hatzichristou DG, Krane RG, MC Kinley JB. Impotence and its medical and psychosocial relates: results of the Massachusetts Male Ageing Study. *J Urol* 151: 54-61, 1994.

2. Kapoor D, Malkin CJ, Channer KS, Jones TH. Androgens, insulin resistance and vascular disease in man. *Clin Endocrinol (Oxf)* 63: 239-250, 2005.

3. Kempler P. Erectile dysfunction. In: *Neuropathies.* Kempler P (ed). Springer Scientific Publisher, Budapest, pp. 123-128, 2002.

4. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metabol* 89: 5462-5468, 2004.

5. Kaplan SA, Meehan AG, Shah A. The age related decrease in testosterone is significantly exacerbated in obese men with the metabolic syndrome. What are the implications for the relatively high incidence of erectile dysfunction observed in these men? *J Urol* 176: 1524-1528, 2006.

6. Haffner SM, Shaten J, Stern MP et al. Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 143: 889-897, 1996.

7. Stellato RK, Feldman HA, Hamdy O, Horton ES, Mc Kinlay JB. Testosterone, sex hormone-binding globulin and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male ageing study. *Diabetes Care* 23: 490-494, 2000.

8. Laaksonen D, Niskanen L, Punnonen K et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle age men. *Diabetes Care* 27: 1036-1041, 2004.

9. Rosen RC, Cappelleri JC, Smith MD, Lipsky J, Pena BM. Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. *Int J Impot Res* 11**:** 319-326, 1999.

10. Kahn RC, Weir GC. Retinopathy. In: *Joslin's Diabetes Mellitus* 13-th ed. Lea & Febiger Waverly Company, 1992.

11. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 39[2 Suppl 1]: S1- S266, 2002.

12. Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *J Clin Endocrinol Metab* 84: 3666-3672, 1999.

13. Henis O, Shahar Y, Steinvil A et al. Erectile dysfunction is associated with severe retinopathy in diabetic men. *Urology* 77: 1133-1136, 2011.

14. Chew SK, Taouk Y, Xie J et al. Relationship between diabetic retinopathy, diabetic macular oedema and erectile dysfunction in type 2 diabetics. *Clin Exp Ophthalmol* 41: 683-689, 2013.

15. Moța M, Lichiardopol C, Moța E, Pănuș C, Pănuș A. Erectile dysfunction in diabetes mellitus. *Rom J Intern Med* 41: 163-177, 2003.

16. Martin-Jabaloyas JM, Quipo-Zaragoza A, Pastor-Hermandez F, Gil-Salom M, Chuan-Nuez P. Testosterone levels in men with erectile dysfunction. *BJU Int* 97: 1278-1283, 2006.

17. Rabijewski M, Zgliczynski W. The high prevalence of testosterone deficiency syndrome and erectile dysfunction in the aging men with diabetes mellitus type 2. *Endocrine Abstracts* 16: P260, 2008.

18. Basar MM, Aydin G, Mert HC et al. Relationship between serum sex steroids and Aging Male Symptoms score and International Index of Erectile Function. *Urology* 66: 597-601, 2005.

19. Rathi M, Ramachandran R. Sexual and gonadal dysfunction in chronic kidney disease. Pathophysiology. *Indian J Endocrinol Metab* 16: 214-219, 2012.

20. Bellinghieri G, Santoro D, Mallamace A, Savica V. Sexual dysfunction in chronic renal failure. *J Nephrol* 21[Suppl. 13]: S113-S117, 2008.

21. Valles-Antuna C, Fernandez-Gomez J, Fernandez-Gonzalez F. Peripheral neuropathy: an underdiagnosed cause of erectile dysfunction. *BJU Int* 108: 1855-1859, 2011.