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ORIGINAL ARTICLE

Hypogonadism among Jordanian men with type 2 diabetes: Prevalence and associated factor

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Abstract *Aims:* Prevalence of hypogonadism is largely unknown in the general population and population of diabetics in Arab countries including Jordan. This study was conducted to determine the prevalence of hypogonadism among men with type 2 diabetes in Jordan and determine its associated factors.
Methods: This cross-sectional study included a total of 1049 consecutive men with type 2 diabetes who attended the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman, Jordan, in the period from August 2008 to February 2009. Data were collected from medical records and using a pre-structured questionnaire. Clinical characteristic, anthropometric measurements and laboratory measurements were obtained. Hypogonadism was defined as total testosterone <3 ng/ml.
Results: Overall, 36.4% of patients with diabetes had total testosterone level <3 ng/ml and 29% had symptoms of androgen deficiency. Of those with serum testosterone level <3 ng/ml, 80.2%

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had symptoms of androgen deficiency. About 16.9% of those with serum testosterone level < 3 ng/ml had primary hypogonadism and 83.1% had secondary hypogonadism. Age, monthly income of less than 500 JD, obesity, and neuropathy were significantly associated with low serum total testosterone level.

Conclusions: The prevalence of hypogonadism among men with type 2 diabetes in Jordan is high. This urgently calls for implementing early and universal screening programs irrespective of symptoms of androgen deficiency to detect those who have low serum total testosterone level at any early stage and to supplement testosterone accordingly.

1. Introduction

The association between hypogonadism and diabetes mellitus has recently received considerable attention [1,2]. Investigators have highlighted the potential metabolic consequences of testosterone decline, showing a potential role of low testosterone on age-associated metabolic changes such as abdominal obesity [3], diabetes and markers of prediabetes [4,5].

Most studies among men with diabetes had defined hypogonadism solely on the basis of testosterone levels [5]. Symptoms of hypogonadism have rarely been considered in combination with biochemical testosterone deficiency [6]. There is an interest in understanding the co-occurrence of symptoms of low testosterone, as well as low testosterone level, because the clinical significance of a low testosterone level alone is unclear [7]. Total testosterone concentrations are determined, to a large extent, by circulating sex hormone-binding globulin (SHBG) concentrations. In the blood of normal men, 44% of total testosterone is bound to SHBG, 2% is unbound [free testosterone] and 54% circulates bound to albumin and other proteins [8].

It is not known whether the lower testosterone levels in diabetics are associated with changes in luteinizing hormone (LH) and follicular stimulating hormone (FSH). Previously published data shows that the commonest form of gonadal dysfunction was hypogonadotropic hypogonadism [9]. Ando et al. [10] reported low total testosterone and normal LH levels in diabetics, whereas Ali et al. [11] found that subjects with diabetic neuropathy had low testosterone and high LH and FSH levels.

The prevalence of hypogonadism is largely unknown in the general population and the population of diabetics in Arab countries, including Jordan. This study was conducted to determine the prevalence of hypogonadism among men with type 2 diabetes in Jordan and its associated factors.

2. Methods

2.1. Subjects

This study comprised a total of 1049 consecutive men with type 2 diabetes who attended the National Center for Diabetes, Endocrinology and Genetics (NCDEG) in Amman, Jordan, between August 2008 and February 2009. The study was approved by the ethical committee of the NCDEG and all patients gave verbal consent to participate in the study. The sample size of 1049 yielded a power of more than 80% at the level of confidence of 95%, and a margin of error of 5%.

2.2. Data collection

During the patients' visits, their demographic characteristics were collected using a pre-structured questionnaire. Data related to the duration of diabetes, medications and clinical history, including the presence of neuropathy, retinopathy and coronary artery disease, were abstracted from medical records. Study participants were asked to complete an Androgen Deficiency in Ageing Male (ADAM) questionnaire. This questionnaire has 88% sensitivity and 60% specificity [12]. A positive response is based on a decrease in libido or the strength of erections, or any three nonspecific questions that may include a decrease in muscle strength, fatigability, mood changes and loss of height.

2.3. Measurements

Weight and height were measured, and body mass index (BMI) was computed by dividing the weight in kilograms by the square of height in meters. Blood pressure was measured using a standardized sphygmomanometer. A trained nurse performed the procedure while the subject was in a sitting position, with the arm at the level of the heart and after 5 min rest.

A venous blood sample (20 ml) was drawn between 8:00 and 10:00 AM after an overnight fast. Blood was withdrawn from the cubital fossa and/or dorsum of the hand veins from each participant, using a disposable syringe. It was injected in the plain and CBC tube; the specimen immediately centrifuged, and serum was aliquoted and stored at −20 °C for total testosterone, free testosterone, SHBG, FSH, LH and prolactin (PRL), HbA1c, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride. Laboratory technicians were blinded to participants' characteristics. Total testosterone was assessed using radioimmunoassay. Free testosterone was assessed using Axsym, which is based on a microparticle enzyme immunoassay. SHBG was tested by means of an immunochemiluminometric assay. LH, FSH and prolactin were measured by chemiluminescent immunometric assays. Glycosylated hemoglobin (HbA1c) was analyzed using a high-performance liquid chromatography (HPLC) method (Bio-Rad). Information concerning HbA1c was adopted from tests made in the NCDEG lab. Total cholesterol, triglyceride, HDL and LDL were assayed through the automated spectrophotometer, enzymatic colorimetric method, COBAS INTEGRA using commercial kits supplied by Roche Diagnostics.

2.4. Definitions

In our study, hypogonadism was defined as total testosterone < 3.0 ng/ml. Symptomatic androgen deficiency was defined

as total testosterone <3.0 ng/ml in addition to a positive response to ADAM questionnaire. Primary hypogonadism was defined as LH >10MIU/ml with total testosterone <3.0 ng/ml, while secondary hypogonadism was defined as LH $\leqslant 10$MIU/ml with total testosterone <3.0 ng/ml.

The diagnosis of DM was based on the American Diabetes Association (ADA) criteria [13]. Nephropathy as diagnosed by the nephrologists (the presence of either microalbuminuria which is defined as, the presence of microalbuminuria $\geqslant 30$–299 mg/24 h urine collection sample or the presence of macroalbuminuria $\geqslant 300$ mg/24 h urine collection sample) [14] was obtained from the patient's record. Retinopathy was defined according to the American Academy of Ophthalmology (AAO) [15]. Patients were classified into non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).

Overweight was defined as BMI 25–29.9 kg/m^2, and obesity was defined as BMI $\geqslant 30$ kg/m^2. Among type 2 diabetic patients, lipid levels were considered as abnormal according to ADA criteria [16]. Hypercholesterolemia refers to a total cholesterol level $\geqslant 200$ mg/dl. HDL was considered low when the level was <40 mg/dl. LDL was considered high when the level $\geqslant 100$ mg/dl. Hypertriglyceridemia was considered high when TG level was $\geqslant 150$ mg/dl. Dyslipidemia was considered present when one or more of the previous abnormalities were found in serum lipids, or if the patient was receiving medication for any of the above conditions.

Among the diabetic patients, hypertension was defined according to ADA criteria 2007 [13]. Coronary heart disease (CHD) was defined as a previous diagnosis of coronary artery disease (CAD) by angiography or ECG, or in terms of current treatment for CAD. Patients with HBA1c $<7\%$ were considered controlled [13].

2.5. Statistical analysis

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS version 15). Data were described using mean and standard deviation for continuous variables and proportions for categorical variables. Univariate analysis of the association between low serum total testosterone level and studied variables were assessed for statistical significance, using Chi-square tests or independent *T*-test, wherever appropriate. Multivariate logistic regression was used to assess the factors associated with low testosterone level. A *P*-value of <0.05 was considered statistically significant.

3. Results

3.1. Participants' characteristics

This study included a total of 1049 patients with type 2 diabetes, aged between 30 and 70 years with a mean age (SD) of 52 (11.2) years. Their socio-demographic, clinical and relevant characteristics are shown in Table 1. The mean (SD) of BMI was 29.9 (5.2) kg/m^2 with about 43.8% of diabetics being obese, and 39.3% overweight. About 28.7% had diabetes for more than 10 years. More than half of the patients (58.7%) were on combination of oral antidiabetic agents and insulin. Most patients (88.3%) were on statins. Two thirds of the diabetic population (69.2%) was on antihypertensive treatment.

Table 1 Socio-demographic, clinical and relevant characteristics of study participants.

Variable	*n* (%)
Age (years), mean (SD) = 52.6 (11.2)	
30–39	178 (16.3)
40–49	242 (22.2)
50–59	299 (27.5)
60–70	370 (34.0)
Education	
Less than university	475 (43.6)
University education	614 (56.4)
Occupation	
Employed	287 (43.3)
Not employed	713 (67.6)
Income (JD)*	
<500 JD	545 (50)
$\geqslant 500$ JD	544 (50)
Body mass index (kg/m^2), mean (SD) = 29.9 (5.2)	
<25 kg/m^2	148 (16.9)
Overweight	428 (39.3)
Obese	477 (43.8)
Smoking	
Non	282 (25.9)
Past	325 (29.8)
Current	482 (44.3)
Hypertension	902 (82.8)
Dyslipidemia	1007 (92.5)
HbA1c, mean (SD) = 8.3 (1.7)	
HbA1c $\leqslant 7$	232 (21.3)
HbA1c > 7	857 (78.7)
Duration of diabetes (years), mean (SD) = 8.1 (6.1)	
$\leqslant 5$	503 (46.2)
6–10	273 (25.1)
>10	313 (28.7)
Diabetic retinopathy	
No diabetic retinopathy	369 (33.9)
Non proliferative diabetic retinopathy	617 (56.7)
Proliferative diabetic retinopathy	103 (9.5)
Diabetic nephropathy	383 (35.2)
Diabetic nephropathy	404 (317)

* 1 JD = 1.41$.

3.2. Prevalence of low testosterone level

Table 2 shows the mean (SD) of serum gonadal hormone levels among patients with type 2 diabetes mellitus, according to age. The mean of serum gonadal hormone levels varied according to age. It seems that total and free testosterone levels decreased with increasing age.

Overall, 36.4% of patients with diabetes had total testosterone level <3 ng/ml and 29% of study participants had symptoms of androgen deficiency. The prevalence of low serum total testosterone was 45% in age group 60–70 years, 37% in age group 50–59 and 34.3% in age group 40–49 and 19.8% in age group 30–39. Table 3 shows the prevalence of low serum testosterone level (Total testosterone <3 ng/ml) for patients with type 2 diabetes mellitus, according to the relevant characteristics. Of those with serum testosterone level <3 ng/ml,

Table 2 The mean (SD) values of serum gonadal hormones level among patients with diabetes (n = 1049) according to age category.

Parameter	30–39	40–49	50–59	60–70	Total
Total testosterone (ng/ml)	4.6 (1.8)	3.8 (1.6)	3.8 (1.8)	3.4 (1.5)	3.8 (1.7)
Free testosterone (pg/ml)	11.8 (5.5)	10.3 (4.2)	9.7 (4.3)	7.8 (3.7)	9.6 (4.5)
Follicle stimulating hormone (MIU/ml)	7.7 (4.3)	7.4 (4.3)	8.5 (6.4)	10.6 (9.2)	8.8 (6.9)
Leuteinizing hormone (MIU/ml)	6.0 (2.3)	6.2 (2.7)	6.6 (3.9)	7.5 (4.8)	6.7 (3.9)
Sex hormone binding globulin (nmol/l)	39.1 (13.6)	36.2 (14.3)	38.0 (16.3)	37.2 (15.7)	37.5 (15.3)
Prolactin (ng/ml)	9.5 (7.1)	10.4 (8.2)	9.4 (6.1)	9.9 (6.6)	9.8 (6.9)

80.2% had symptoms of androgen deficiency. About 16.9% of those with serum testosterone level <3 ng/ml had primary hypogonadism, and 83.1% had secondary hypogonadism.

3.3. Multivariate analysis of factors associated with low testosterone level

In the multivariate analysis, the only variables that remained significantly associated with low serum total testosterone level were age, income, body mass index and neuropathy (Table 4). Compared to patients in the age group 30–39 years, patients aged 40–49 years (OR = 1.89), 50–59 years (OR = 1.96), and 60–69 years (OR = 2.57) were more likely to have low total testosterone level. Those who had a monthly income of less than 500 JD were more likely to have low total testosterone level (OR = 1.76) than those who had a monthly income of more than, or equal to 500 JD. Compared to patients with obesity, those who had BMI <25 kg/m^2, and those that were overweight, were less likely to have low total testosterone level. Diabetic neuropathy was associated with the increased odds of low total testosterone level.

4. Discussion

In the present study, 36.4% of patients with type 2 diabetes had a total testosterone level of <3 ng/ml, and 29% of study participants had symptoms of androgen deficiency. It is difficult to compare the study findings with those reported in other studies, because of the differences in age of participants, cut-points used to define hypogonadism, and duration and complication of diabetes.

In a large cohort of 574 men with type 2 diabetes with a mean age of 65 and mean duration of diabetes of 10 years, Mathis and his colleagues [17] found that 43% had total testosterone levels <10 nmol/l. In the United Kingdom, a cross-sectional study of 355 men with type 2 diabetic aged >30 showed that 17% of diabetic men had overt hypogonadism with total testosterone <8 nmol/1, and a further 25% had symptoms of hypogonadism associated with a total testosterone level of between 8 and 12 nmol/l [6]. In Spain, Corrales et al. [18] used a combination of clinical and hormonal criteria to define androgen deficiency and to analyze the relationship between the androgen environment and glucose metabolism in 55 type 2 diabetic men (63.6 ± 7.9 years, mean ± SD). Low plasma levels of total testosterone ($\leqslant$3.4 ng/ml) and free testosterone ($\leqslant$11 pg/ml) were found in 20% and 54.5% of diabetic men respectively. Another cross-sectional study from Brazil showed that free and total testosterone levels were subnormal in 46% and 34% of diabetics, respectively [19].

Of those with hypogonadism, 16.9% had primary hypogonadism (LH > 10 MIU/ML) and 83.1% had secondary hypogonadism (LH < 10 MIU/ML); suggesting that hypogonadotropic hypogonadism is the predominant type of hypogonadism in our diabetic subjects. This finding was not consistent with the findings revealed by Ali et al. [11] who found high serum and urinary FSH and LH among diabetics with low serum total and serum free testosterone levels. However, Tenover et al. [20] found that the majority of hypogonadal men over the age of 60 had low, or inappropriately normal LH levels. On the other hand, Chandel et al. [21] found that LH and FSH concentrations in type 2 diabetic patients with low free testosterone concentrations were in the normal range. Our study reported a higher prevalence of hypogonadotropic hypogonadism (low LH and FSH) levels than that reported by Kapoor et al. [6] who found that 7% had hypogonadotropic hypogonadism and lower prevalence of primary hypogonadism (high LH and FSH) levels which was seen in 26% of patients with type 2 diabetes compared to 16.9% of those who were hypogonadal in our study who had a high level of LH. A study carried out in Taiwan [22] showed that the prevalence of both androgen deficiency and the prevalence of symptomatic androgen deficiency were 24.1% and 12%, respectively.

Both cross-sectional and longitudinal studies indicate that testosterone levels decrease with age [23]. Our study showed that total testosterone was inversely related to age. A higher prevalence of low total testosterone was seen in men aged between 60 and 70 years, which is in agreement with the findings of Grossmann et al. [17] who reported that 43% of men of the same age had low total testosterone. Our findings were similar to those of Corrales et al. [18] who found that the fraction of diabetic men with a subnormal level of total testosterone increased with age. Our findings were consistent with the findings revealed by Grossmann et al. [24] and Fukui et al. [25]. Grossmann et al. [24] found that those with low testosterone levels were older than individuals with testosterone levels in the normal range.

In agreement with previous studies [6,19,24,26–28], our study showed a significant association between BMI and low serum total testosterone level. On the other hand, in a cross-sectional study, Tripathy et al. [29], reported that there is no relationship between total testosterone and BMI.

Regarding smoking, our study showed no significant association between smoking and low testosterone levels in logistic regression analysis. This result is in agreement with previously published data [25,28,30].

Serum lipids were not significantly associated with low total testosterone in logistic regression analysis, a finding which is in agreement with the findings of several other investigators who reported no significant correlation between serum lipids and

Table 3 Prevalence of low serum testosterone level (total testosterone < 3 ng/ml) for patients with type 2 diabetes mellitus according to relevant characteristics.

Variable	Total testosterone level		*P*-value
	$\geqslant 3$ ng/ml	< 3 ng/ml	
Age			< 0.005
30–39	138 (80.2)	34 (19.8)	
40–49	151 (65.7)	79 (34.3)	
50–59	182 (63.0)	107 (37.0)	
60–70	192 (54.7)	159 (45.3)	
Income			< 0.005
< 500	290 (55.8)	230 (44.2)	
$\geqslant 500$	373 (71.5)	149 (28.5)	
Education			< 0.005
Less than university	255 (56.3)	198 (43.7)	
University	408 (69.3)	181 (30.7)	
Body mass index (kg/m^2)			< 0.004
< 25	120 (70.6)	50 (29.4)	
Overweight	276 (66.7)	138 (33.3)	
Obese	267 (58.3)	191 (41.7)	
Smoking			
Non-smoker	179 (64.9)	97 (35.1)	0.004
Past-smoker	178 (58.0)	129 (42.0)	
Current	306 (66.7)	379 (36.4)	
Hypertension			0.055
Yes	536 (62.5)	322 (37.5)	
No	127 (69.0)	57 (31.0)	
Dyslipidemia			0.493
Yes	612 (63.7)	349 (36.3)	
No	51 (63.0)	30 (37.0)	
Diabetic retinopathy (DR)			0.002
No DR	249 (69.9)	107 (30.1)	
Non proliferative DR	364 (61.7)	226 (38.3)	
Proliferative DR	50 (52.1)	46 (47.9)	
Diabetic nephropathy			0.070
Yes	217 (60.4)	142 (39.6)	
No	446 (65.3)	237 (34.7)	
Diabetic neuropathy			< 0.005
Yes	210 (54.4)	176 (45.6)	
No	453 (69.1)	203 (30.9)	
Duration of diabetes			< 0.005
$\leqslant 5$ years	339 (70.3)	143 (29.7)	
6–10 years	168 (65.1)	90 (34.9)	
> 10 years	156 (51.7)	146 (48.3)	
HbA1c			
HbA1C $\leqslant 7$	158 (70.5)	66 (29.5)	0.009
HbA1C > 7	505 (61.7)	313 (38.3)	

Table 4 Multivariate analysis of factors associated with low testosterone level.

Variable	OR (95% CI)	*P*-value
Age		
30–39	1	
40–49	1.89 (1.18, 3.04	0.008
50–59	1.96 (1.23, 3.10)	0.004
60–70	2.57 (1.63, 2.57)	< 0.005
Income		
< 500	1.76 (1.35, 2.29)	< 0.005
$\geqslant 500$	1	
Body mass index (kg/m^2)		
< 25 kg/m^2	0.73 (0.49, 1.08)	0.124
Overweight	0.71 (0.54, 0.95)	0.022
Obese	1	
Diabetic neuropathy		
Yes	1.39 (1.05, 1.84)	0.021
No	1	

hypogonadism [25,28]. In contrast, some other studies showed that lower HDL cholesterol and higher triglyceride levels were significantly correlated with hypogonadism among diabetics [17,31,32].

Serum testosterone levels have been reported to be lower in men with hypertension [27]. The association observed between serum total testosterone level and both systolic and diastolic blood pressure was not significant among our study participants. These findings are consistent with those reached by others [30,31].

In the present study, there was no significant association between the serum testosterone level and HbA1c concentration. This finding is consistent with the results obtained by other studies [24,33], while opposing what was found by Kapoor et al. [6]. Our findings also contradict the finding of the study undertaken by Fukui et al. [34], who found that total testosterone concentrations correlated positively with HbA1c concentrations.

The association observed between hypogonadism and the duration of diabetes was not significant in our study. However, this effect is difficult to determine in patients with type 2 diabetes. A plausible explanation for this is that type 2 diabetes may be silent for many years before clinical recognition. This finding is consistent with data from a number of studies [5,25,33].

Surprisingly, in the present study, we found a statistically significant association between monthly income and hypogonadism. This finding is consistent with work done by Susan et al. [35]. A possible explanation for this association is that a monthly income of less than 500 JDs may function as a marker for poorer health access, increased stress, adverse health behaviors, and impoverished neighborhood environment. Wong et al. [36] found that having a lower personal income was independently associated with the increased risk of having androgen deficiency.

A significant association between low testosterone level and the presence of diabetic neuropathy was found in this study. These results are in agreement with previously published data [17,25]. Ali et al. [11] reported a significantly low serum total testosterone level in the neuropathic diabetic patients.

Several limitations have to be considered in the interpretation of this study. This is a cross-sectional design, making it impossible to determine the causality of whether the diabetes preceded or followed the decline in serum testosterone level.

In conclusion, given the large numbers of individuals with diabetes in Jordan, the number of diabetic patients with low serum testosterone is undoubtedly enormous. This urgently calls for implementing early, universal screening programs, irrespective of the symptoms of androgen deficiency, in order to detect those who have low serum total testosterone level at any early stage and to supplement testosterone accordingly. We recommend screening all type 2 diabetics for androgen

levels in health care settings, and referring them to endocrinologists accordingly, as well as establishing a hormonal base line for patients with type 2 diabetes to compare with in the future.

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