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Prevalence of erectile dysfunction among Saudi type 2 diabetic patients

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Abstract. – OBJECTIVES: The present study aimed to determine the prevalence and etiology of erectile dysfunction in Saudi type 2 diabetic patients

PATIENTS AND METHODS: 429 Saudi type 2 diabetic male patients aged more than 30 years were recruited. Total and bio-available serum testosterone, sex hormone binding globulin and free testosterone levels were measured by ELISA-IBL GMBH Germany.

RESULTS: 47 (12.6%) subjects had hypogonadism with total testosterone < 8 nmol/l and 109 (29.3%) had possible hypogonadism with a total testosterone between 8 and 12 nmol/l. Similarly, using bioavailable levels, 30 (8%) men had overt hypogonadism with bioavailable testosterone < 2.5 nmol/l and 89 (33.9%) men had possible hypogonadism with bioavailable testosterone between 2.5-4 nmol/l; while 266 (71.6%) patients with free testosterone < 0.255 nmol/l had hypogonadism. BMI and waist circumference were both significantly negatively correlated with testosterone levels in Saudi type 2 diabetic men.

CONCLUSIONS: Testosterone levels are frequently low in Saudi men with type 2 diabetes and majority of these patients have symptoms of hypogonadism. The prevalence of erectile dysfunction (ED) was 86.7% in diabetic men with low testosterone level of 8-12 nmol/L. Obesity is an associated factor with low testosterone levels and ED in Saudi type 2 diabetic patients.

Key Words:
Hypogonadism, Erectile dysfunction, Type 2 diabetes, Saudi population.

Introduction

Diabetes mellitus is a leading health problem and world is witnessing a pandemic. The estimated number of patients with diabetes was 371 million in 2012 and will reach approximately 552 million by 2030[1]. The prevalence of diabetes among 30-70 years age group in Saudi Arabia is one of the highest in the world[2]. Aging population, high consanguinity, obesity, together with socioeconomic changes and westernization has resulted in the great rise in the prevalence[3].

Insulin resistance is an important feature of type 2 diabetes. Subnormal free testosterone concentrations in association with inappropriately low LH and FSH concentrations and a normal response to GnRH of LH and FSH in type 2 diabetes were first described in 2004[4]. This association of hypogonadotropic hypogonadism (HH) with type 2 diabetes has now been confirmed in several studies and is present in 25-40% of these men[5,6]. It is being increasingly recognized that low testosterone level in men is associated with reduced insulin sensitivity and type 2 diabetes[7]. Furthermore, male hypogonadism effects up to 50% of men diagnosed with type 2 diabetes[8]. Obesity is associated with type 2 diabetes and reduced testosterone levels[9]. Hypogonadotrophic hypogonadism is linked to major conditions associated with insulin resistance, type 2 diabetes and metabolic syndrome. This is of interest since inflammatory mechanisms may have a cardinal role in the pathogenesis of insulin resistance[10].

Erectile Dysfunction (ED) is a common and distressing complication of diabetes. Advancing age, duration of diabetes, poor glycaemic control, hypertension, hyperlipidemia, sedentary lifestyle, and smoking are associated with ED in diabetic patients[11]. Hypogonadism is a clinical condition comprising both symptoms and biochemical evidence of testosterone deficiency[12]. According to the Endocrine Society clinical practice guidelines for androgen deficiency syndromes in adult men, total testosterone (TT) level less than or equal to 10.4 nmol/l (300 ng/dL) along with signs and symptoms, the patient is diagnosed as hypogonadal[13]. Literature is lacking

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in demonstrating the prevalence of hypogonadism in type 2 diabetic patients in Saudi Arabia. Therefore, the aim of this study was to assess the prevalence and etiology of erectile dysfunction in Saudi type 2 diabetic male patients based on both biochemical and clinical criteria[14] .

Patients and Methods

This study was conducted in the University Diabetes Centre, King Saud University, Riyadh, Saudi Arabia during the period Aug 2009 to Nov 2011. 429 Saudi type 2 diabetic male patients, age more than 30 years were recruited. A written informed consent was obtained and Institutional Review Board approval was obtained. Patients with a history of any inflammatory disease or infection with elevation of C-reactive protein more than 10 mg/l, patients who were receiving hormone replacement therapy or suffering with any neoplastic disorder were excluded from the study.

In adult men, testosterone release has a diurnal rhythm, in which testosterone levels are highest in the early morning and lowest in the evening. Therefore, hormonal assessments were made between 8:00 to 11:00 am[4]. Patients were screened initially with a questionnaire detailing their medical history, smoking status, and concomitant medications. Height, weight, and waist circumference were measured and BMI calculated. Blood pressure was recorded in the sitting position as standard recommendations.

Patients were asked to complete an Androgen Deficiency in the Aging Male (ADAM) validated questionnaire (Table I)[14]. This is a 10-item screening questionnaire used to evaluate androgen deficiency in aging males. A positive response is based on decreased libido or strength of erections or any nonspecific questions including fatigability, decreased muscle strength, mood changes, and loss of height. Hypogonadism was confirmed if: either Q1, or Q2, or Q7 was answered yes or 3 positive answers together for the remaining questions: (Q3, Q4, Q5, Q6, Q8, Q9 and Q10). A venous blood sample (20 ml) was collected; serum samples were obtained by centrifugation and frozen at -20°C for analysis. Total testosterone, FSH and LH were measured by the enzyme-linked immunosorbent assay technique (Roche Diagnostics, Mannheim, Germany). A total testosterone level < 8 nmol/l was considered to be low, and a level between 8 and 12 nmol/l was considered to be borderline low. Bioavailable testosterone below the normal range (< 2.5 nmol/l) is consistent with overt hypogonadism in young healthy men, whereas a significant proportion of patients with bioavailable testosterone between 2.5 and 4 nmol/l are also hypogonadal as shown in the study by Leifke et al[15]. A free testosterone level < 0.25 nmol/l was taken as low[16]. In patients with a low testosterone level (total testosterone < 12 nmol/l), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by enzyme- linked immunosorbent assay technique (Roche Diagnostics, Mannheim, Germany). Free testosterone and bioavailable testosterone were calculated[17]. SHBG was measured by ELISA (IBL International GmbH, Hamburg, Germany).

Statistical Analysis

Data were analyzed using the SPSS software package version 17.0 (SPSS Inc., Chicago, IL USA). Continuous variables were expressed as Mean ± Standard Deviation. Categorical variables were expressed as percentages and frequencies. *t*-test was used to estimate differences in quantitative values and chi-square test for cate-

Table I. Androgen Deficiency in Aging Male [ADAM] questionnaire.

ADAM questionnaire	Frequency of yes answer: n (%)
Q1. Do you have decreased libido or sex drive?	164 (38.2%)
Q2. Do you have lack of energy?	155 (36.1%)
Q3. Do you have decreased strength and/or endurance?	155 (36.1%)
Q4. Have you lost weight?	16 (3.7%)
Q5. Have you noticed a decreased “enjoyment of life”?	46 (10.7%)
Q6. Are you sad and/or grumpy?	43 (10.0%)
Q7. Are your erections less strong?	350 (81.6%)
Q8. Have you noticed deterioration in playing sports?	87 (20.3%)
Q9. Are you falling asleep after dinner?	72 (16.8%)
Q10. Has there been deterioration in work performance?	53 (12.4%)

gorical ones. Odds ratio was used to express the strength of association between different risk factors of hypogonadism among subjects of the study cohort. *p* value lower than 0.05 and 95% confidence interval were used to demonstrate the level of significance. Graph Pd software was used to plot for different risk factors.

Results

A total of 600 Saudi type 2 diabetic patients, who fulfilled the inclusion criteria were initially recruited in this cross-sectional study. Of the 600 patients screened, only 429 had complete data and were included for final statistical analysis. The baseline data is presented in Table II. Mean age was 55.29 ± 8.67 years (range 35-80). The mean testosterone levels (total, free, and bioavailable, respectively) were 13.92, 0.25, and 5.74 nmol/l (Table II).

The age distribution and mean testosterone levels (total, free, and bio-available, respectively) were < 40 years (21 men; 4.9%): 13.99 ± 4.67, 0.29 ± 0.09, and 6.78 ± 2.13 nmol/l; 40-49 years (91 men; 21.2%): 14.60 ± 5.89, 0.29 ± 0.12, and 6.89 ± 2.87 nmol/l; 50-59 years (162 men; 37.8%): 13.90 ± 5.31, 0.24 ± 0.12, and 5.48 ± 2.72 nmol/l; 60-69 years (144 men; 33.6%): 13.59 ± 4.92, 0.22 ± 0.11, and 5.17 ± 2.53 nmol/l; and > 69 years (11 men; 2.6%): 13.05 ± 3.91, 0.25 ± 0.14, and 5.83 ± 3.21 nmol/l. There was a strong association between bio-available and free testosterone ($r = 0.983$; $p < 0.0001$). 11.3% (47 men) had total testosterone < 8 nmol/land 25.5% (109 men) had total testosterone between 8 and 12 nmol/l, 7.1% (30 men) had bioavailable testosterone < 2.5 nmol/l, and 20.8% (89 patients) had bioavailable testosterone between 2.5 and 4 nmol/l, and 62.1% (266 men) had free testosterone < 0.255 nmol/l (Figure 1). The age distribution of low testosterone levels is shown in (Figures 2 and 3).

Prevalence of Symptoms and Low Testosterone Levels (Hypogonadism)

Using the definition of hypogonadism as the combination of symptoms (positive ADAM score Table I, Figure 4) in addition to a low testosterone level, 12.6% (47 subjects) had overt hypogonadism with total testosterone < 8 nmol/l and 29.3% (109 men) had possible hypogonadism with total testosterone between 8 and 12 nmol/l. Similarly, using bioavailable levels, 8% (30 men) had overt hypogonadism with bioavailable testosterone < 2.5 nmol/l and 33.9% (89 men) had possible hypogonadism with bioavailable testosterone between 2.5 and

Table II. Baseline characteristics.

Parameters	Number	Minimum	Maximum	Mean ± SD
Age (years)	429	35	80	55.3 ± 8.67
Diabetes duration (years)	429	1	40	13.8 ±7.93
Weight (kg)	429	43	147.2	82.3 ± 15.05
Height (cm)	429	145	186	167.7 ± 6.57
BMI (kg/m^2)	429	16	44.8	29.28 ± 4.66
Waist circumference (cm)	429	68	140	103.2 ± 11.53
Systolic BP (mmHg)	429	95	170	132.2 ± 13.3
Diastolic BP (mmHg)	429	43	107	75.0 ± 8.88
HbA1c (%)	429	4.8	14.1	8.59 ± 1.52
Fasting blood glucose (mmol/L)	429	3.6	20.6	8.87 ± 2.93
LDL (mmol/L)	426	0.68	6.34	2.50 ± 0.8
HDL (mmol/L)	426	0.4	2.03	1.05 ± 0.24
Cholesterol (mmol/L)	428	2.23	8.91	4.33 ± 0.96
TG (mmol/L)	427	0.44	11.70	1.77 ± 1.09
CRP (mg/dl)	423	0	24.0	1.02 ± 2.47
FSH (U/L)	421	0.1	98.54	7.56 ± 8.34
LH (U/L)	421	0.1	40.66	6.74 ± 4.48
PSA µg/L)	353	0	11.22	1.01 ± 1.07
Total testosterone (nmol/L)	416	0.6	36.71	13.92 ± 5.24
Free Testosterone (nmol/L)	409	0.012	0.788	0.245 ± 0.12
SHBG (nmol/L)	423	4.0	175.8	50.26 ± 33.65
Bio-available testosterone (nmol/L)	409	0.25	19.30	5.74 ± 2.75
Albumin (g/L)	422	30.70	50.60	42.90 ± 3.30

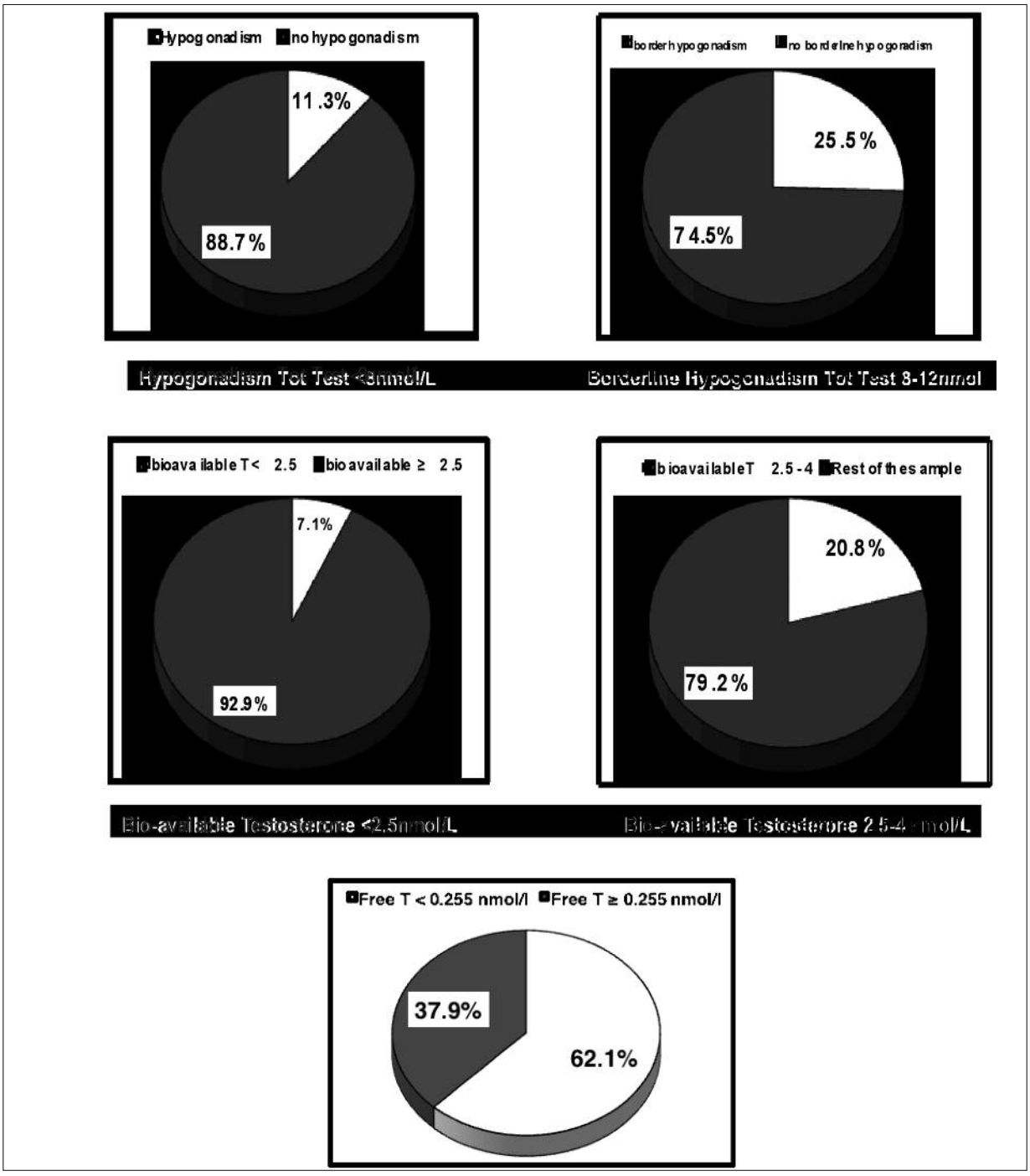

Figure 1. Prevalence of low testosterone levels.

4 nmol/l; 71.6% (266 patients) had free testosterone < 0.255 nmol/l. The prevalence of hypogonadism stratified by decades is shown in Table III.

ED was the most common symptom occurring in > 86.7% of the diabetic men with low testosterone level of 8-12 nmol/L (Table III). Of the men with ED and hypogonadism (total testosterone < 12 nmol/l or bioavailable testosterone < 4 nmol/l or free testosterone < 0.255 nmol/l), 43.9% had reduced libido and 27.1% had other symptoms of hypogonadism. Only 29.3% of the hypogonadal men had ED without any other associated symptom (Table III).

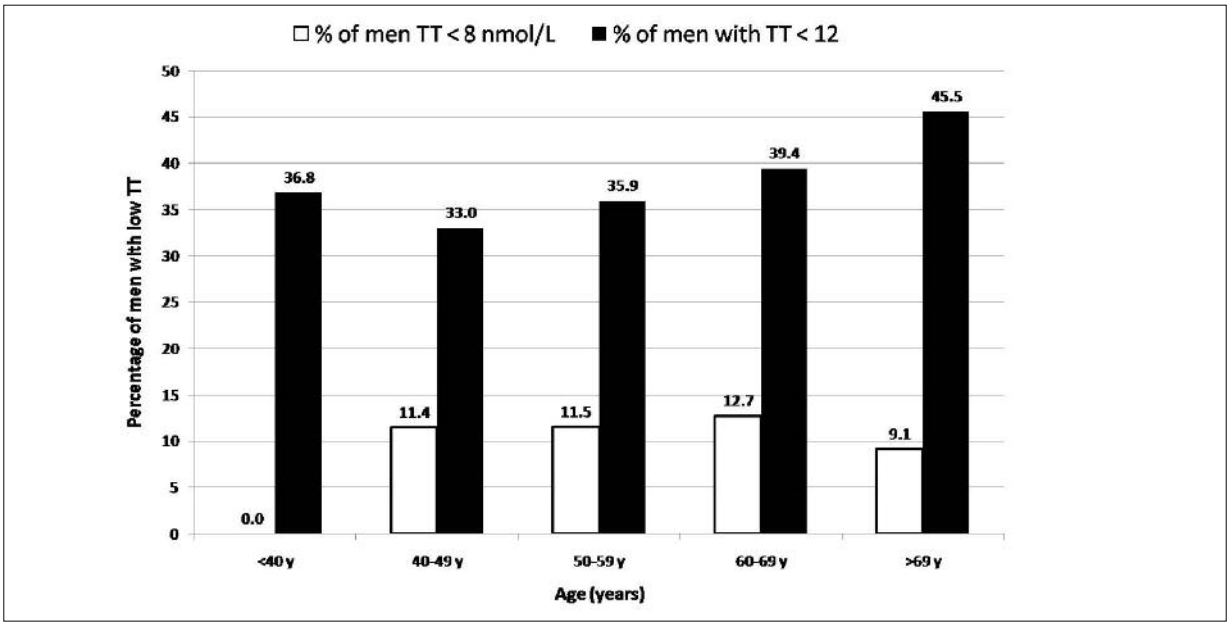

Figure 2. Percentage and age distribution of T2 DM patients with low levels of TT.

Primary hypogonadism (FSH or LH > 10 IU/l) was seen in 22.8%, and 7.1% had secondary hypogonadism (FSH or LH < 2 IU/l, who were further investigated and found to have no other abnormality in pituitary hormones and MRI pituitary); 70.1% had hypogonadism with normal levels of gonadotrophins.

Sex Hormones and Body Composition

Total testosterone significantly and negatively correlated with both BMI ($r = –0.164$; $p = 0.001$) and waist circumference ($r = –0.126$; p 0.010). SHBG also significantly correlated with both BMI ($r = –0.189$; $p < 0.0001$) and waist circumference ($r = –0.114$; $p = 0.019$). Bioavailable

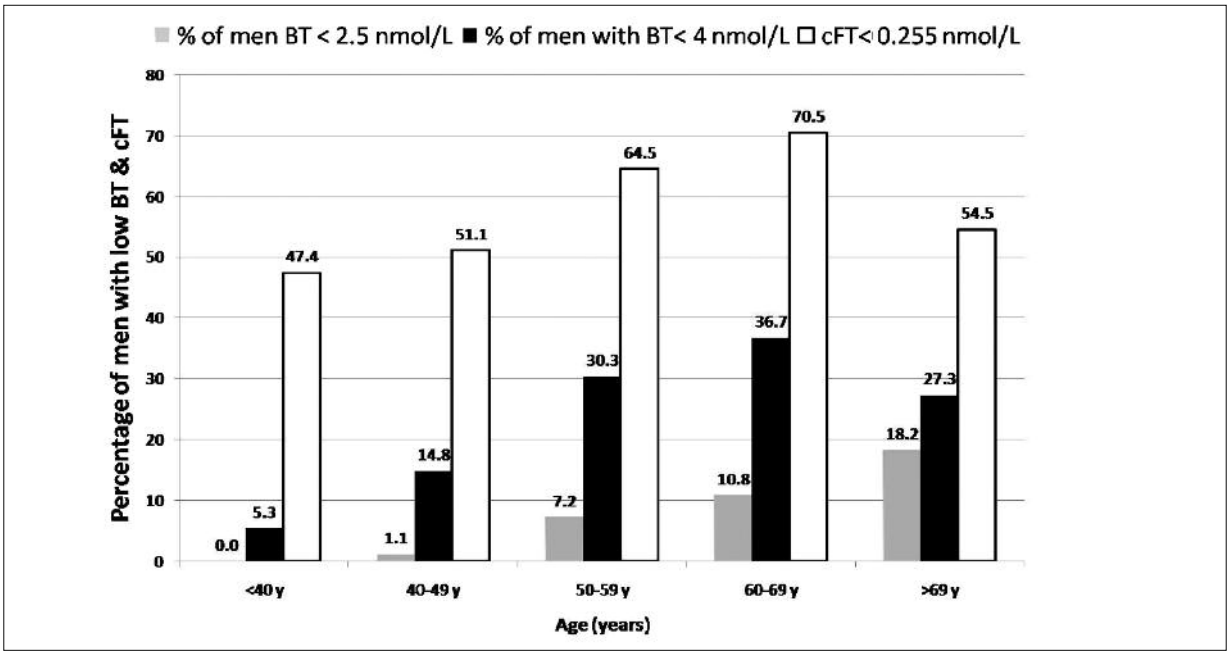

Figure 3. Percentage and age distribution of T2 DM patients with low levels of BT and cFT.

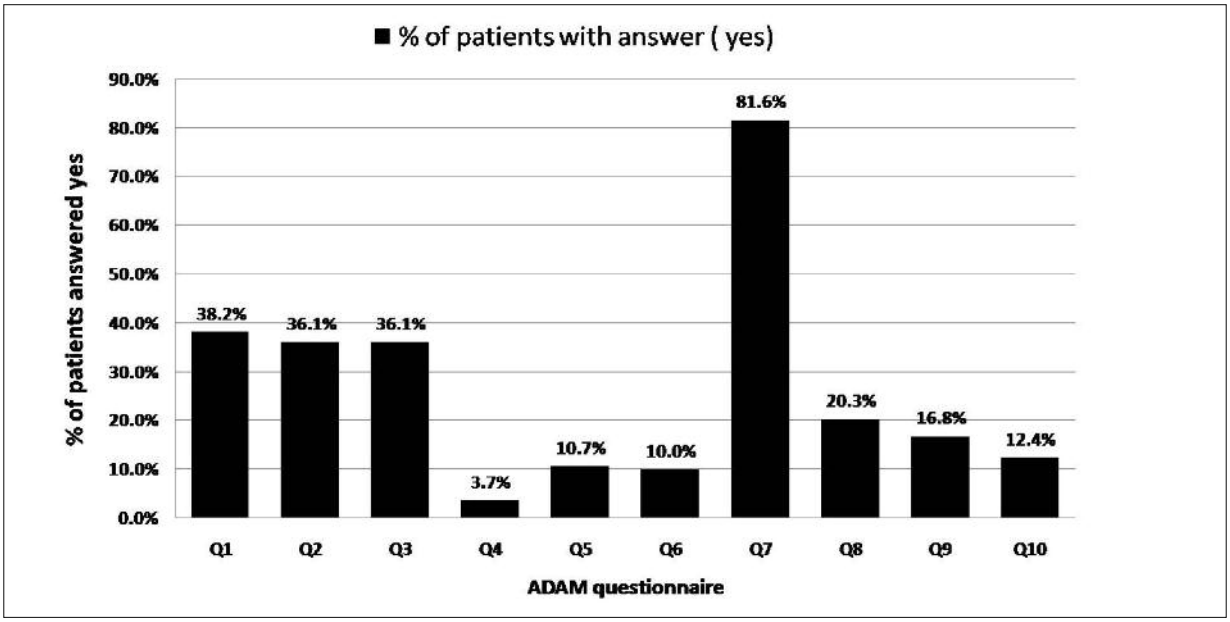

Figure 4. Percentage of patients with affirmed ADAM questions.

testosterone correlated with waist circumference (r = –0.013±; p = 0.787) and with BMI (r = 0.036±; p = 0.463) Total and bioavailable testosterone levels were significantly lower in men with BMI > 30 kg/m^2 or waist circumference > 94 cm (Table IV, Figure 5). Among the whole sample 68.8% of the patients were noted to have metabolic syndrome. The prevalence was higher 75.8% in patients with hypogonadism than non hypogonadism 64.6% (Sensitivity = 91% Specificity = 14% Overall accuracy = 42%).

HbA1C, Blood Pressure, Smoking, and Testosterone Levels

When both A1C and BMI were adjusted for in regression analysis, BMI (p = 0.001) and not

Table III. Percentages of men with symptoms of hypogonadism by hormones levels and deciles.

Parameter	Reduced Libido	ED	Fatigability	Decreased muscle strength	Mood changes
Hormones					
TT < 8 nmol/L	34	78.7	27.7	25.5	8.5
TT 8-12 nmol/L	40	86.7	42.9	41.9	9.5
TT > 12 nmol/L (Control)	39.7	81.7	36.1	36.5	9.9
BT > 2.5 nmol/L	27.6	79.3	24.1	27.6	3.4
BT 2.5-4 nmol/L	41.2	81.2	37.6	37.6	10.6
BT > 4 nmol/L (control)	22.4	82.9	37.8	36.4	9.9
cFT < 0.255 nmol/L	38.2	79.1	36.2	36.2	8.3
cFT > 0.255 nmol/L (Control)	38.6	87.6	37.7	35.7	11.7
Percentages of men with symptoms of hypogonadism by age					
< 40 years	9.5	38.1	19	28.6	14.3
40-49 years	34.8	76.4	36.7	33.3	10
50-59 years	38.3	85.8	38.9	38.3	11.7
60-69 years	43.8	86.1	34.7	36.1	7.6
> 69 years	54.5	100	45.5	45.5	9.1

ED: Erectile dysfunction.

Table IV. Risk factors of hypogonadism among type 2 diabetes.

Risk factor	Odds ratio and 95% CI	*p*-value
DM duration > 10 years	3.39 (1.90-6.06)	< 0.0001
Obesity	2.88 (1.36-6.07)	0.004
Hypertension	2.83 (1.58-5.07)	< 0.0001
HbA1c more than 8%	2.77 (1.56-4.94)	< 0.0001
Waist > 94 cm	2.69 (1.46-4.96)	0.001
Overweight	2.08 (1.03-4.19)	0.038
Hypertriglyceridemia	2.01 (1.06-3.83)	0.030

A1C (p = 0.636) was a significant predictor of total testosterone. Similarly, only waist circumference was a significant predictor of total testosterone (p = 0.014) when both waist circumference and A1C were compared against total testosterone. Total testosterone was significantly lower in men with A1C > 8% (Table IV, Figure 5). There was no significant correlation between A1C and bioavailable or free testosterone (p = 0.843) or between A1C and SHBG (p = 0.065). A1C was also associated with waist circumference (r = 0.126; p = 0.009) and BMI (r = 0.151; p = 0.002). 59.9% of the patients had a history of hypertension. There was no significant association between testosterone levels and history of hypertension (p = 0.578; r = 0.027). Of the patients, 23.1% were ex-smokers and 10.3% were current smokers. There was no significant association between history of smoking and bioavailable or total testosterone levels (r = 0.072; p = 0.149).

Discussion

In this study we found that, testosterone levels are frequently low in Saudi men with type 2 diabetes and majority of these patients have symptoms of hypogonadism. The prevalence of erectile dysfunction was 86.7% in diabetic men with low testosterone level of 8-12 nmol/L. Previous studies[4] showed that about one-third of type 2 diabetic men have low serum testosterone levels, but these studies had not correlated with clinical symptoms. Furthermore, the present study has demonstrated, in line with Dhindsa et al[4] that low testosterone levels cannot be explained solely by the lower levels of SHBG associated with insulin resistance. In this study, we found that, a high proportion of diabetic men have low levels of bioavailable and free testosterone. The findings also showed that obesity and visceral adiposity as assessed by both BMI and waist circumference, were negatively associated with low levels of testosterone.

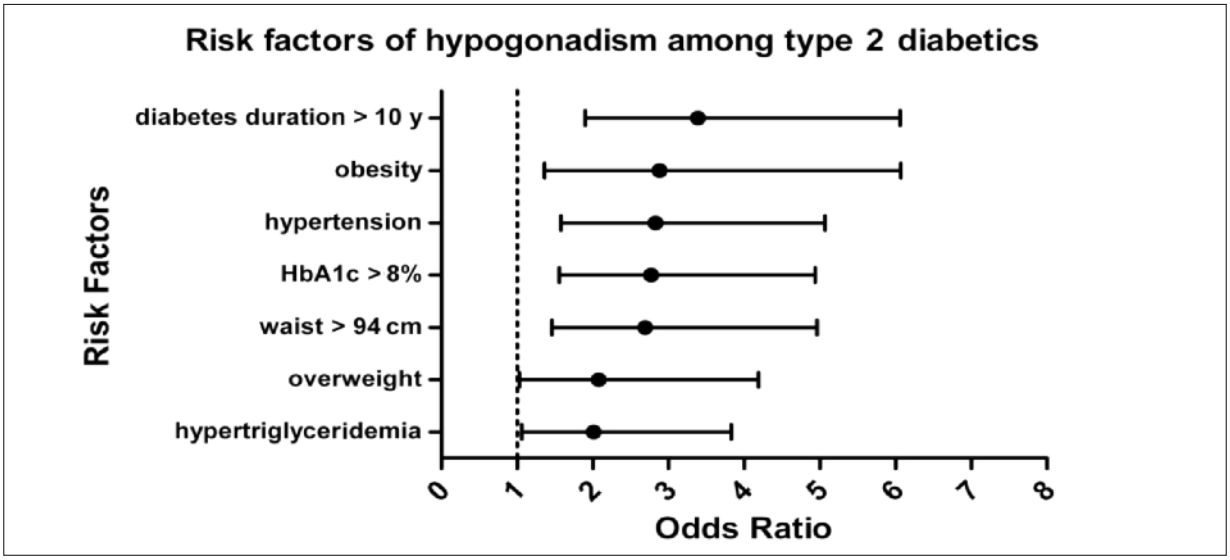

Figure 5. Risk factors of hypogonadism among type 2 diabetes.

In fact, guidance on the diagnosis of hypogonadism in diabetes is important. There is no widely accepted agreement as what constitutes the level of testosterone below which treatment is to be considered. On the basis of normal ranges and international recommendations, our results show that 11.3% of the diabetic men had overt hypogonadism with total testosterone < 8 nmol/l, and a further 25.5% had symptoms of hypogonadism associated with total testosterone between 8 and 12 nmol/l. The confounding factor of low SHBG with insulin resistance may have resulted in lower total testosterone levels in this population. However, the finding of a similar prevalence of hypogonadism using bioavailable testosterone and the wide range of SHBG levels (4-175.8 nmol/l) suggest that, this may not be an explanation. It may be that each patient needs to be assessed individually, but the importance of assessing bioavailable testosterone is also demonstrated.

Aging is associated with a decline in testosterone levels in men[12]. In the Harman et al[18], report on aging, 8, 12, 19, and 28% of men aged > 40, 50, 60, and 70 years, respectively had serum total testosterone levels below the normal range (< 11.3 nmol/l). Using the criteria of Harman et al[18], study we found a higher prevalence of hypogonadism across all age-groups (42, 44, 39, and 56% in the age-groups 40-49, 50-59, 60-69, and 70-79 years respectively). The mean total and bioavailable testosterone levels in Saudi diabetic males are also lower in all age-groups compared with data found by Leifke et al [15] in healthy non-obese males and by Muller et al[19]. Dhindsa et al[4] have similarly shown low total and free testosterone levels in type 2 male diabetics.

The frequencies of hypogonadal symptoms were similar in all defined groups of low testosterone. It is important to note that the ADAM questionnaire lacks specificity and is useful only in the presence of a low testosterone level. An interesting finding was that male diabetics with ED had lower bioavailable and free testosterone levels. This further underlines the importance of measuring testosterone levels in diabetic men.

The question, thus, arises as to why diabetic men have lower testosterone levels. Klinefelter's syndrome, the most frequent form of primary hypogonadism is associated with insulin resistance and diabetes[20]. In our work, approximately one-third of the hypogonadal men had either primary or secondary hypogonadism. The rest of the hypogonadal group had low testosterone levels with normal gonadotrophins. It is possible that these men have either secondary hypogonadism as was defined in the study by Dhindsaet al[4] where in men with low testosterone levels and normal or low gonadotrophins were thought to have hypogonadotrophic hypogonadism or a combination of primary and secondary hypogonadism as observed with aging.

We found that testosterone levels inversely correlated with waist circumference and BMI. A credible explanation for this is the hypogonadal obesity cycle[7]. Essentially, visceral adipocytes have a high activity of the enzyme aromatase, which converts testosterone to estrogen. Testosterone inhibits the enzyme lipoprotein lipase, which takes up free fatty acids into adipocytes[21]. Lower levels of testosterone result in increased triglyceride levels in adipocytes, which promote further adipocyte proliferation and hence higher aromatase activity. Testosterone levels are further lowered as a result of leptin resistance at the hypothalamic-pituitary and testicular levels, causing reduced LH release and testosterone secretion[7,22]. It is known that a reduction in the degree of obesity results in an elevation of testosterone levels with larger effects seen in more obese men with greater degrees of weight loss[23,24]. A retrospective analysis of men with impaired glucose tolerance from the diabetes prevention program (DPP) cohort showed that men randomized to lifestyle modification had a modest but significant + 1.5 nmol/L (43 ng/dL) increase in their testosterone levels coincident with 7.8 kg weight loss[25] Recent observational evidence from the EMAS cohort suggests that ≥ 15% of weight loss is required to reactivate the hypothalamic-pituitary-testicular axis[26]. Visceral obesity is an established cause of insulin resistance. We have shown that glycemic control was significantly associated with both BMI and waist circumference. Our findings agree with other studies[27].

Serum testosterone levels have been reported to be lower in men with hypertension[28]. Our findings showed a significant association between testosterone levels and hypertension. Testosterone status is becoming increasingly recognized as essential in the assessment and treatment of men with ED. It has been established that men with ED who do not respond to sildenafil frequently have hypogonadal levels of testosterone[29], and testosterone replacement therapy converts 60% of sildenafil non responders into responders[30]. Furthermore, there is evidence that testosterone replacement therapy improves

insulin resistance, glycemic control, cholesterol levels, and waist circumference in diabetic men with low testosterone levels[31].

Conclusions

The prevalence of erectile dysfunction (ED) was 86.7% in diabetic men with low testosterone level of 8-12 nmol/L. Obesity is an important associated factor with low testosterone levels and ED in Saudi type 2 diabetic patients. This research demonstrates that a significant number of Saudi type 2 male diabetics have testosterone insufficiency and symptoms of hypogonadism. It also illustrates that the diagnosis of hypogonadism is difficult in that the symptoms are nonspecific especially in diabetic men. The current study findings also show that bioavailable testosterone measurement is an important adjunct to the assessment of borderline hypogonadism in diabetes, eliminating the confounding effect of variable SHBG levels. As the frequency of subnormal free testosterone concentrations in our study population is high 62.1%, we believe that, free testosterone concentration should be measured in every male patient with type 2 diabetes. This is consistent with the Endocrine Society guidelines. An Androgen Deficiency in Aging Male (ADAM) questionnaire should be administered in every patient with a low testosterone so that the presence of clinical hypogonadism can be established and ED timely managed.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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