Original Article

Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study

Ayman A. Al Hayek, Yousef S. Khader[1], Sahar Jafal[2], Nahla Khawaja[2], Asirvatham A. Robert[3], Kamel Ajlouni[2]

Department of Endocrinology and Diabetes, Diabetes Education Unit, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia, [1]Department of Community Medicine, Faculty of Medicine, Jordan University of Science and Technology, Irbid, [2]National Center of Diabetes, Endocrinology and Genetics, Amman, Jordan, [3]Research Center, Medical Affairs, Sultan Bin Abdulaziz Humanitarian City, Riyadh, Saudi Arabia

Address for correspondence: Mr. Ayman A. Al Hayek, Department of Endocrinology and Diabetes, Diabetes Education Unit, Prince Sultan Riyadh Military Medical City, P. O. Box 7897, Riyadh 11159, Saudi Arabia. E-mail: ayman.alhayek@yahoo.com

ABSTRACT

Background: A high prevalence of low serum testosterone (LST) in men with type 2 diabetes have been reported worldwide. The aim of this study was to determine the prevalence and associated factors of LST in men with type 2 diabetes. **Materials and Methods:** This was a cross-sectional study, conducted among 1,089 men (aged 30-70 years) with type 2 diabetes who consecutively attended a major diabetes center in Amman, Jordan, between August 2008 and February 2009. The patients' demographic characteristics were collected using a prestructured questionnaire. Duration of diabetes, smoking habits, presence of retinopathy, neuropathy, and nephropathy were collected from the medical records. All participants were asked to complete the Androgen Deficiency in Ageing Male (ADAM) questionnaire. Venous blood sample was collected to test for total testosterone (TT), free testosterone (FT), sex hormone binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), serum lipids, and glycosylated hemoglobin (HbA1c). LST was defined as TT <3 ng/ml. **Results:** Overall, 36.5% of patients with diabetes had TT level <3 ng/ml and 29% had symptoms of androgen deficiency. Of those with serum testosterone level <3 ng/ml, 80.2% had symptoms of androgen deficiency, 16.9% had primary hypogonadism (HG), and 83.1% had secondary HG. Univariate analysis showed a significant relationship between age, income, education, body mass index (BMI), smoking, duration of diabetes, diabetic nephropathy, diabetic neuropathy, and HbA1c. Multivariate logistic regression analysis indicated age, income, BMI, and diabetic neuropathy as the independent risk factors of LST. **Conclusions:** The prevalence of LST among men with type 2 diabetes is high. Age, income, BMI, and diabetic neuropathy were found to be the independent risk factors for LST.

Key words: Diabetes mellitus, low serum testosterone, prevalence

INTRODUCTION

Diabetes mellitus (DM) affects an estimated 285 million people worldwide. This number is expected to reach 438 million by the year 2030, with two-thirds of all cases occurring in low- to middle-income countries.[1] Asians develop diabetes at a younger age, at lower degrees of obesity, and at much higher rates given the same amount of weight gain compared with Western populations.[2] The prevalence of type 2 diabetes is high in Jordan and more than half of the patients with diabetes have unsatisfactory metabolic control.[3]

The association between low serum testosterone (LST) and DM has recently received substantial attention.[4,5] Studies have reported that men with type 2 DM (T2DM) have a high prevalence of LST.[6-8] Further, reduced total testosterone (TT) levels have been associated with insulin resistance and subsequent risk for developing T2DM.[9,10] The main symptoms of LST are reduced libido/erectile dysfunction, reduced muscle mass and strength, increased adiposity, osteoporosis/low bone mass, depressed mood, fatigue, low energy, and impaired quality of life.[11,12]

Access this article online	
Quick Response Code:	Website: www.jfcmonline.com
	DOI: 10.4103/2230-8229.122006

Researchers have highlighted the potential metabolic consequences of testosterone decline on age-associated metabolic changes such as abdominal obesity, diabetes, and markers of prediabetes.[13-15] hypogonadism (HG) is a clinical condition consisting of both symptoms and biochemical signs of testosterone deficiency. However, many studies in men with diabetes have defined LST solely on the basis of testosterone levels. Symptoms of HG have rarely been considered in combination with biochemical testosterone deficiency.[16] There is a growing interest in understanding the concurrence of symptoms of low testosterone and a low testosterone level since the clinical significance of a low testosterone level alone is unclear.[17] TT concentrations are determined, to a large extent, by the circulating sex hormone binding globulin (SHBG) concentrations. In the blood of normal men, 44% of TT is bound to SHBG, 2% is unbound (free testosterone (FT)), and 54% circulates bound to albumin and other proteins.[18] 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 show that the commonest form of gonadal dysfunction was hypogonadotropic HG.[19] Ando *et al.*,[20] reported low TT and normal LH levels in diabetics; whereas, Ali *et al.*,[21] found that subjects with diabetic neuropathy had low testosterone, high LH and FSH levels. The prevalence of LST is largely unknown both in the diabetic population and in the general population in Arab countries, including Jordan. This study was conducted to determine the prevalence of LST in men with T2DM and its associated factors.

MATERIALS AND METHODS

A total of 1,089 men (aged 30-70 years) with type 2 diabetes who consecutively attended at a major diabetes center in Amman, Jordan, between August 2008 and February 2009 were included in the study. Patients with any inflammatory disease or infection and already receiving hormone replacement therapy were excluded. Informed verbal consent was obtained from all the patients to participate in the study, and the local research ethics committee approved the protocol. The sample size of 1,089 yielded a power of more than 80% at the confidence level of 95%, and a 5% margin of error.

The respondents were purposely and conveniently selected according to their availability during their routine visit to the outpatient clinics. The patients' demographic characteristics were collected using a prestructured questionnaire. Information on the duration of diabetes, presence of retinopathy, neuropathy, and nephropathy was collected from their medical records. Smoking habits were assessed by dividing men into categories of current, former, and never smokers. Study participants were asked to complete the androgen deficiency in ageing male (ADAM) questionnaire. This questionnaire has 88% sensitivity and 60% specificity.[22] 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.

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. Hypertension was defined as elevated systolic (≥140 mmHg) or diastolic (≥90 mmHg) blood pressure. 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 into the plain complete blood count tube; the specimen immediately centrifuged, and serum was aliquoted and stored at −20°C to determine TT, FT, SHBG, FSH, LH, prolactin (PRL), glycosylated hemoglobin (HbA1c), total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride. Laboratory technicians were blinded to participants' characteristics. TT was assessed using radioimmunoassay. FT was assessed using Axsym, which is based on a microparticle enzyme immunoassay.[16] SHBG was tested by means of an immunochemiluminometric assay. LH, FSH, and PRL were measured by chemiluminescent immunometric assays. HbA1c was analyzed using high performance liquid chromatography (HPLC) method (Bio-Rad). Information concerning HbA1c was adopted from tests made in the National Center for Diabetes, Endocrinology, and Genetics 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.

In this study, LST was defined as TT <3.0 ng/ml and TT used as reference parameter to define LST.[8,23,24] Symptomatic androgen deficiency was defined as TT <3.0 ng/ml in addition to a positive response to ADAM questionnaire. Primary HG was defined as LH >10 MIU/ml with TT <3.0 ng/ml, while the secondary HG was defined as LH <2 MIU/ml with TT <3.0 ng/ml.[16]

The diagnosis of DM was based on the American Diabetes Association (ADA) criteria.[25] Nephropathy as diagnosed by the nephrologists (the presence of micro albuminuria

which is defined as, the presence of micro albuminuria ≥30-299 mg/24 h urine collection sample or the presence of macro albuminuria ≥300 mg/24 h urine collection sample)[26] was obtained from the patient's record. The diabetic neuropathies are heterogeneous, affect different parts of the nervous system, and present with diverse clinical manifestations. They may be focal or diffuse.[27] Retinopathy was defined according to the American Academy of Ophthalmology (AAO).[28] Patients were classified into nonproliferative 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 ≥30 kg/m^2. Among type 2 diabetic patients, lipid levels were considered abnormal according to ADA criteria. Hypercholesterolemia referred to a total cholesterol level ≥200 mg/dl. HDL was considered low when the level was <40 mg/dl. LDL was considered high when the level ≥100 mg/dl. Hypertriglyceridemia was considered high when TG level was ≥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. Patients with HbA1c <7% were considered controlled.[25]

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS version 15). In addition to descriptive analysis, Chi-square tests or independent *t*-test were done to find out associations. Multivariate logistic regression was carried out to assess the factors associated with low testosterone level. $P < 0.05$ was considered statistically significant.

RESULTS

This study included a total of 1,089 patients with type 2 diabetes, aged between 30 and 70 years with a mean age of 52 ± 11.2 years. The sociodemographic and clinical characteristics of participants are shown in Table 1. The mean BMI was 29.9 ± 5.2 kg/m^2 and 43.8% of diabetics were 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 a 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 2 shows the variations in the mean serum gonadal hormone levels by different age groups. It seems that total and FT levels decreased with increasing age. Overall, 36.5% of patients with diabetes had TT level <3 ng/ml and 29% of study participants had symptoms of androgen deficiency. Table 3 indicates the prevalence of LST level (TT <3 ng/ml) by groups of different variables. The prevalence of low total serum testosterone was 45.4% in age group 60-70 years, 37.8% in age group 50-

Table 1: Demographic, clinical, and relevant characteristics of study participants (*n*=1,089)

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 (26.3)
Not employed	802 (73.6)
Income (JD)	
<500 JD	545 (50.1)
P500 JD	544 (49.9)
Body mass index (kg/m^2), mean (SD)=29.9 (5.2)	
<25 kg/m^2	184 (16.9)
Overweight	428 (39.3)
Obese	477 (43.8)
Smoking	
Never	282 (25.9)
Former	325 (29.8)
Current	482 (44.3)
Hypertension	
Hypertension	902 (82.8)
No hypertension	187 (17.2)
Dyslipidemia	
Dyslipidemia	1002 (92)
No dyslipidemia	87 (8)
HbA1c, mean (SD)=8.3 (1.7)	
HbA1c≤7	232 (21.3)
HbA1c>7	857 (78.7)
Duration of diabetes (years), mean (SD)=8.1 (6.1)	
≤5	503 (46.2)
6-10	273 (25.1)
>10	313 (28.7)
Diabetic retinopathy	
No diabetic retinopathy	369 (33.9)
Nonproliferative diabetic retinopathy	617 (56.6)
Proliferative diabetic retinopathy diabetic nephropathy	103 (9.5)
Diabetic nephropathy	
Diabetic nephropathy	383 (35.2)
No diabetic nephropathy	706 (64.8)
Diabetic neuropathy	
Diabetic neuropathy	404 (37.1)
No diabetic neuropathy	685 (62.9)

SD: Standard deviation, JD: Jordanian dinar

Table 2: The mean (SD) values of serum gonadal hormones level among patients with diabetes according to age group

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)

SD: Standard deviation

59, and 34.3% in age group 40-49, and 19.1 in age group 30-39 [Table 3]. Of those with serum testosterone level <3 ng/ml, 80.2% had symptoms of androgen deficiency, about 16.9% had primary HG, and 83.1% had secondary HG. The univariate analyses indicated significant differences among the age groups ($P = 0.005$), income ($P = 0.005$), education ($P = 0.005$), BMI ($P = 0.004$), smoking ($P = 0.004$), duration of diabetes ($P = 0.005$), diabetic nephropathy ($P = 0.005$), diabetic neuropathy ($P = 0.005$), and HbA1c ($P = 0.009$).

Multivariate analysis indicated age, income, BMI, and neuropathy as the factors significantly associated with a low total serum testosterone level [Table 4]. Compared to 30-39 years age group, patients aged 40-49 years (Odds ratio (OR = 1.89), 50-59 years (OR = 1.96), and 60-69 years (OR = 2.57) were more likely to have a low level of TT. Those who had a monthly income of less than 500 JD were more likely to have low TT levels (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 who were overweight; were less likely to have a low level of TT. Diabetic neuropathy increased the odds of a low TT level.

DISCUSSION

Reports that have clearly established that LST is common and that at least 25% of men with type 2 diabetes have LST with inappropriately low LH and FSH concentrations are on the increase. Another 4% have subnormal testosterone concentrations with higher LH and FSH concentrations.[10,29,30] Due to a higher prevalence of low testosterone in diabetics, the possibility that LST might contribute to diabetes-related sexual dysfunction has recently been reevaluated.[31] The present study found that 36.5% of patients with T2DM had a TT level of <3 ng/ml, and 29% had symptoms of androgen deficiency.

The term secondary (hypogonadotropic) HG denotes an inadequate release of gonadotropin-releasing hormone (GnRH) and is characterized by low-normal or low levels of FSH, LH, and testosterone. The present study indicated that TT, FT, and SHBG decreased with age. Several cross-sectional studies and systemic analyses from various countries have reported that type 2 diabetes is associated with LST. However, these studies reported differences in LST levels with the varying ages of participants, cut-off points used to define HG, method of analysis, duration, and complication of diabetes are dissimilar. A study from Australia reported that 43% of type 2 diabetes patients had TT levels <10 nmol/l.[9] In the United Kingdom, a cross-sectional study of 355 men with type 2 diabetic aged >30 showed that 17% had HG with TT <8 nmol/1, and a further 25% had symptoms of HG associated with a TT level between 8 and 12 nmol/l.[16] A recent study from Egypt reported 33.2% HG in type 2 diabetes patients.[5] Another cross-sectional study from Brazil showed that FT and TT levels were subnormal in 46 and 34% of diabetics, respectively.[32] Considering the importance of the situation, The Endocrine Society recommends measuring the testosterone of patients with type 2 diabetes on a routine basis.[29,33]

The present study reports that of the LST subjects, 16.9% had primary HG and 83.1% had secondary HG, suggesting that hypogonadotropic HG is the predominant type of HG in our diabetic subjects. This finding is not consistent with the findings revealed by Ali *et al.*,[21] which found high serum and urinary FSH and LH in diabetics with low total serum and serum FT levels. However, Tenover *et al.*,[34] 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.*,[35] found that LH and FSH concentrations in type 2 diabetic patients with low FT concentrations were in the normal range. Further, a recent study showed that high prevalence of HG and depressive symptoms were found in patients who had been newly diagnosed T2DM.[36]

Both cross-sectional and longitudinal studies have indicated decreased testosterone levels in the older population compared to the younger.[9,11,37] Our study found a

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

Variables	Total testosterone level		*P* value
	≥3 ng/ml	<3 ng/ml	
Age			
30-39	144 (80.9)	34 (19.1)	0.005
40-49	159 (65.7)	83 (34.3)	
50-59	186 (62.2)	113 (37.8)	
60-70	202 (54.6)	168 (45.4)	
Income			
<500	242 (44.4)	303 (55.6)	0.005
≥500	386 (71.0)	158 (29.0)	
Education			
Less than university	269 (55.6)	206 (43.4)	0.005
University	426 (69.4)	188 (30.6)	
Body mass index (kg/m^2)			
<25	128 (69.6)	56 (30.4)	0.004
Overweight	142 (33.2)	286 (66.8)	
Obese	197 (41.3)	280 (58.7)	
Smoking			
Never	183 (64.9)	99 (35.1)	0.004
Former	188 (57.8)	137 (42.1)	
Current	260 (53.9)	222 (46.0)	
Hypertension			
Yes	338 (37.5)	564 (62.5)	0.055
No	128 (68.4)	59 (31.5)	
Dyslipidemia			
Yes	363 (36.2)	639 (63.8)	0.493
No	52 (59.8)	35 (40.2)	
Duration of diabetes			
≤65 years	354 (70.4)	149 (29.6)	0.005
6-10 years	97 (35.5)	176 (64.5)	
>10 years	152 (48.6)	161 (51.4)	
Diabetic retinopathy (DR)			
No DR	260 (70.5)	109 (29.5)	0.070
Non proliferative DR	381 (61.7)	236 (38.2)	
Proliferative DR	54 (52.4)	49 (47.6)	
Diabetic nephropathy			
Yes	152 (39.7)	231 (60.3)	0.005
No	460 (65.1)	246 (34.8)	
Diabetic neuropathy			
Yes	184 (45.5)	220 (54.4)	0.005
No	468 (68.3)	217 (31.7)	
HbA1c			
HbA1c≤7	162 (69.8)	70 (30.2)	0.009
HbA1c>7	329 (38.4)	528 (61.6)	

SD: Standard deviation

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
≥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	

OR: Odds ratio; CI: Confidence interval

significant association between TT and age. A higher prevalence of low TT was seen in men aged between 60 and 70 years, which is in agreement with the previous finding that HG was frequently associated with T2DM, at least in the 6th decade.[31] In this study, there was a lower prevalence in age group 30-39. The frequency of diabetes with HG in those aged less than 40 years could be due to the fact that most diabetic patients in this age group have by type I, and not T2DM.[31]

Surprisingly, in the present study, there was a statistically significant association between monthly income and LST. This finding is consistent with the work done by Hall *et al*.[38] A possible explanation for this association is that a lower monthly income may function as a marker for poorer access to health, increased stress, adverse health behaviors, and impoverished neighborhood environment. Wong *et al*.,[39] found that a lower personal income was independently associated with the increased risk of having androgen deficiency.

Many studies have addressed the relationship between BMI and LST of patients with T2DM. The outcomes of these studies are controversial. Some studies have shown a significant association between BMI and LST level.[15,40] In contrast, there was a study that reported no relationship between TT and BMI.[19] However, the present study observed a significant association between BMI and LST levels. A recent study that examined the prevalence of LST in obese and diabetic men found that around 44% of diabetic and 33% of age-matched nondiabetic men had subnormal FT concentrations. Forty percent of obese men and 50% of obese diabetic men had subnormal FT concentrations. Thus, obesity is associated with a high prevalence of HG, and the presence of diabetes adds to that risk.[41] However, a study reported that the presence of LST was not entirely dependent upon obesity because 25% of nonobese patients (31% of lean and 21% of overweight) also had HG.[13]

DM is strongly associated with microvascular complications such as retinopathy, nephropathy, and neuropathy resulting in organ and tissue damage in approximately one-third to one-half of people with the disease.[42,43] Our study also found that more than one-third of the diabetes subjects had a microvascular complication, and no significant differences were observed in the study on the prevalence of LST among the subjects with retinopathy and nephropathy. However, a significant association was found in diabetic neuropathy subjects. This is in agreement with other studies which found that a low total serum testosterone level was associated with diabetic neuropathic patients.[9,21,44]

The prevalence of LST was higher in subjects with a longer duration of DM. However, multivariate analysis showed no association with duration of diabetes which is in agreement with previous studies.[45]

Most cross-sectional studies have shown a positive association between smoking and total or FT levels.[46,47] Further, cessation of smoking decreased the testosterone levels of men followed for idiopathic infertility.[47] The mechanisms by which cigarette smoking may increase testosterone levels are uncertain.[48] Multivariate analysis indicated no significant association between smoking and total or FT levels, which is in agreement with previously published data.[44,49]

Research shows that serum testosterone levels have been reported to be lower in men with hypertension.[50] The present study also found a higher prevalence of LST in the diabetic subjects with hypertension. However, total serum testosterone level and hypertension did not indicate any significant association in multivariate analysis. These findings are consistent with those reached by others.[51]

The present study reports that subjects with dyslipidemia had a higher prevalence of LST than subjects without dyslipidemia. However, serum lipids were not significantly associated with low TT in multivariate analysis, which is in agreement with the findings of several other investigators who reported no significant relationship between serum lipids and LST.[44,52] In contrast, some other studies showed that lower HDL cholesterol and higher triglyceride levels were significantly correlated with LST in diabetics.[9,51,53]

In the present study, multivariate analysis did not find an association between the serum testosterone level and HbA1c concentration, which is consistent with the results obtained by some studies,[9,54] while it is in contrast with those by Kapoor *et al*.[16] Our findings also contradict those of the study undertaken by Fukui *et al*.,[55] in which TT concentrations correlated positively with HbA1c concentrations.

There are few limitations in the study. Firstly, this was a cross-sectional design, which made it impossible to determine whether diabetes preceded or followed the decline in serum testosterone level. Secondly, FT was assessed using Axsym, which is based on microparticle enzyme immunoassay. Thirdly, the study examined a limited number of risk factors in a single center.

In conclusion, given the large number of individuals with diabetes, the number of diabetic patients with LST is undoubtedly enormous. What is required is an urgent implementation of early universal screening programs, irrespective of the symptoms of androgen deficiency, in order to detect those with a low total serum testosterone level at an early stage and supplement testosterone accordingly. We recommend the screening of all type 2 diabetics for androgen levels in healthcare settings for referral to endocrinologists. Establishing a hormonal base line for patients with T2DM is also vital so that a comparison of the situation could be made in the future.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas. Epidemiology and Mobidity. In: International Diabetes Federation. Available from: http://www.idf.org/ [Last accessed on 2011 March 1].
2. Chan JC, Malik V, Jia W, Kadowaki T, Yajnik CS, Yoon KH, *et al*. Diabetes in Asia: Epidemiology, risk factors, and pathophysiology. JAMA 2009;30:2129-40.
3. Ajlouni K, Khader YS, Batieha A, Ajlouni H, El-Khateeb M. An increase in prevalence of diabetes mellitus in Jordan over 10 years. J Diabetes Complications 2008;22:317-24.
4. George JT, Veldhuis JD, Tena-Sempere M, Millar RP, Anderson RA. Exploring the pathophysiology of hypogonadism in men with type 2 diabetes: Kisspeptin-10 stimulates serum testosterone and LH secretion in men with type 2 diabetes and mild biochemical hypogonadism. Clin Endocrinol (Oxf) 2013;79:100-4.
5. Ghazi S, Zohdy W, Elkhiat Y, Shamloul R. Serum testosterone levels in diabetic men with and without erectile dysfunction. Andrologia 2012;44:373-80.
6. Kohler TS, Kim J, Feia K, Bodie J, Johnson N, Makhlouf A, *et al*. Prevalence of androgen deficiency in men with erectile dysfunction. Urology 2008;71:693-7.
7. Rezvani MR, Saadatjou SA, Sorouri S, Hassanpour Fard M. Comparison of serum free testosterone, luteinizing hormone and follicle stimulating hormone levels in diabetics and non-diabetics men- a case-control study. J Res Health Sci 2012;12:98-100.
8. Tamler R, Deveney T. Hypogonadism, erectile dysfunction, and type 2 diabetes mellitus: What the clinician needs to know. Postgrad Med 2010;122:165-75.
9. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, *et al*. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 2008;93:1834-40.
10. Soriguer F, Rubio-Martin E, Fernandez D, Valdes S, Garcia-Escobar E, Martin-Nunez GM, *et al*. Testosterone, SHBG and risk of type 2 diabetes in the second evaluation of the Pizarra cohort study. Eur J Clin Invest 2012;42:79-85.
11. Dandona P, Rosenberg MT. A practical guide to male hypogonadism

in the primary care setting. Int J Clin Pract 2010;64:682-96.
12. Zhang XW, Liu ZH, Hu XW, Yuan YQ, Bai WJ, Wang XF, *et al*. Androgen replacement therapy improves psychological distress and health-related quality of life in late onset hypogonadism patients in Chinese population. Chin Med J (Engl) 2012;125:3806-10.
13. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462-8.
14. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, *et al*. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care 2004;27:1036-41.
15. Saboor Aftab SA, Kumar S, Barber TM. The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism. Clin Endocrinol (Oxf) 2013;78:330-7.
16. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: Correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007;30:911-7.
17. Harman SM. Testosterone in older men after the Institute of Medicine Report: Where do we go from here? Climacteric 2005;8:124-35.
18. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: Binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981;53:58-68.
19. Tripathy D, Dhindsa S, Garg R, Khaishagi A, Syed T, Dandona P. Hypogonadotropic hypogonadism in erectile dysfunction associated with type 2 diabetes mellitus: A common defect? Metab Syndr Relat Disord 2003;1:75-80.
20. Ando S, Rubens R, Rottiers R. Androgen plasma levels in male diabetics. J Endocrinol Invest 1984;7:21-4.
21. Ali ST, Shaikh RN, Ashfaqsiddiqi N, Siddiqi PQ. Serum and urinary levels of pituitary: Gonadal hormones in insulin-dependent and non-insulin-dependent diabetic males with and without neuropathy. Arch Androl 1993;30:117-23.
22. Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D, *et al*. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000;49:1239-42.
23. Kim S, Kwon H, Park JH, Cho B, Kim D, Oh SW, *et al*. A low level of serum total testosterone is independently associated with nonalcoholic fatty liver disease. BMC Gastroenterol 2012;12:69.
24. Shores MM, Moceri VM, Gruenewald DA, Brodkin KI, Matsumoto AM, Kivlahan DR. Low testosterone is associated with decreased function and increased mortality risk: A preliminary study of men in a geriatric rehabilitation unit. J Am Geriatr Soc 2004;52:2077-81.
25. Standards of medical care in diabetes – 2007. Diabetes Care 2007;30 Suppl 1:S4-41.
26. Gross JL, de Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelmanovitz T. Diabetic nephropathy: Diagnosis, prevention, and treatment. Diabetes Care 2005;28:164-76.
27. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, *et al*. Diabetic neuropathies: A statement by the American Diabetes Association. Diabetes Care 2005;28:956-62.
28. Wilkinson CP, Ferris FL 3rd, Klein RE, Lee PP, Agardh CD, Davis M, *et al*. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. Ophthalmology 2003;110:1677-82.
29. Dandona P, Dhindsa S. Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab 2011;96:2643-51.
30. Ogbera AO. Relationship between serum testosterone levels and features of the metabolic syndrome defining criteria in patients with type 2 diabetes mellitus. West Afr J Med 2011;30:277-81.
31. Corona G, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, *et al*. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res 2006;18:190-7.
32. Rhoden EL, Ribeiro EP, Teloken C, Souto CA. Diabetes mellitus is associated with subnormal serum levels of free testosterone in men. BJU Int 2005;96:867-70.
33. Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, *et al*. Testosterone therapy in adult men with androgen deficiency syndromes: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2006;91:1995-2010.
34. Tenover JS, Matsumoto AM, Plymate SR, Bremner WJ. The effects of aging in normal men on bioavailable testosterone and luteinizing hormone secretion: Response to clomiphene citrate. J Clin Endocrinol Metab 1987;65:1118-26.
35. Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P. Testosterone concentration in young patients with diabetes. Diabetes Care 2008;31:2013-7.
36. Corona G, Giorda CB, Cucinotta D, Guida P, Nada E. Gruppo di studio SUBITO-DE. The SUBITO-DE study: Sexual dysfunction in newly diagnosed type 2 diabetes male patients. J Endocrinol Invest 2013 [Epub ahead of print].
37. Betancourt-Albrecht M, Cunningham GR. Hypogonadism and diabetes. Int J Impot Res 2003;15 Suppl 4:S14-20.
38. Hall SA, Esche GR, Araujo AB, Travison TG, Clark RV, Williams RE, *et al*. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. J Clin Endocrinol Metab 2008;93:3870-7.
39. Wong SY, Chan DC, Hong A, Woo J. Prevalence of and risk factors for androgen deficiency in middle-aged men in Hong Kong. Metabolism 2006;55:1488-94.
40. Bastounis EA, Karayiannakis AJ, Syrigos K, Zbar A, Makri GG, Alexiou D. Sex hormone changes in morbidly obese patients after vertical banded gastroplasty. Eur Surg Res 1998;30:43-7.
41. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, *et al*. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010;33:1186-92.
42. UK Prospective Diabetes Study (UKPDS). VIII. Study design, progress and performance. Diabetologia 1991;34:877-90.
43. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Phys Ther 2008;88:1322-35.
44. Fukui M, Soh J, Tanaka M, Kitagawa Y, Hasegawa G, Yoshikawa T, *et al*. Low serum testosterone concentration in middle-aged men with type 2 diabetes. Endocr J 2007;54:871-7.
45. Ganesh HK, Vijaya Sarathi HA, George J, Shivane VK, Bandgar T, Menon PS, *et al*. Prevalence of hypogonadism in patients with type 2 diabetes mellitus in an Asian Indian study group. Endocr Pract 2009;15:513-20.
46. Laaksonen DE, Niskanen L, Punnonen K, Nyyssonen K, Tuomainen TP, Valkonen VP, *et al*. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: A prospective cohort study. J Clin Endocrinol Metab 2005;90:712-9.
47. Trummer H, Habermann H, Haas J, Pummer K. The impact of cigarette smoking on human semen parameters and hormones. Hum Reprod 2002;17:1554-9.
48. Barbieri RL, Gochberg J, Ryan KJ. Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast *in vitro*. J Clin Invest 1986;77:1727-33.
49. Oh JY, Barrett-Connor E, Wedick NM, Wingard DL. Endogenous sex hormones and the development of type 2 diabetes in older men and women: The Rancho Bernardo study. Diabetes Care 2002;25:55-60.
50. Phillips GB, Jing T, Heymsfield SB. Relationships in men of sex hormones, insulin, adiposity, and risk factors for myocardial infarction. Metabolism 2003;52:784-90.
51. Corona G, Mannucci E, Petrone L, Balercia G, Paggi F, Fisher AD, *et al*. NCEP-ATPIII-defined metabolic syndrome, type 2 diabetes mellitus, and prevalence of hypogonadism in male patients with sexual dysfunction. J Sex Med 2007;4:1038-45.
52. Diaz-Arjonilla M, Schwarcz M, Swerdloff RS, Wang C. Obesity, low testosterone levels and erectile dysfunction. Int J Impot Res 2009;21:89-98.

53. Stanworth RD, Kapoor D, Channer KS, Jones TH. Dyslipidaemia is associated with testosterone, oestradiol and androgen receptor CAG repeat polymorphism in men with type 2 diabetes. Clin Endocrinol (Oxf) 2011;74:624-30.
54. Dandona P, Dhindsa S, Chaudhuri A, Bhatia V, Topiwala S. Hypogonadotrophic hypogonadism in type 2 diabetes. Aging Male 2008;11:107-17.
55. Fukui M, Tanaka M, Hasegawa G, Yoshikawa T, Nakamura N. Association between serum bioavailable testosterone concentration and the ratio of glycated albumin to glycated hemoglobin in men with type 2 diabetes. Diabetes Care 2008;31:397-401.

How to cite this article: Al Hayek AA, Khader YS, Jafal S, Khawaja N, Robert AA, Ajlouni K. Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study. J Fam Community Med 2013;20:179-86.
Source of Support: Nil, **Conflict of Interest:** None declared.