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The association of hypogonadism with type 2 diabetes mellitus and obesity

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ABSTRACT

Prevalence of hypogonadism was higher among patients with comorbid conditions, such as type 2 diabetes mellitus and obesity. To assess the relationship of hypogonadism with diabetes mellitus and obesity based on positive symptoms and low testosterone level in Iraqi men and to identify the factors that associated with low serum testosterone level. A case control study included 200 patients and divided into two groups; Case group included 100 patients who were a known case of type 2 diabetes (type 2 diabetes) and control group included 100 persons who attended for reasons other than diabetes. All the study patients were investigated for total testosterone, FSH, and LH hormones. SHBG and glycated hemoglobin was done for case group only. Ten milliliters of venous blood sample were taken between 8 – 10 AM. Total testosterone level was low in 56% of case group compared to 19% in control group, and this difference was significant. Means of LH, and FSH were significantly lower in diabetic patients than that in controls. Prevalence of low free testosterone level was significantly increasing with II increasing in BMI level and in-patient who had high waist circumference. we notes that the prevalence of low free testosterone level was significantly increasing with increasing in duration of diabetes and in patient who had high HbA1c level. There were statistical significant associations between low mood, erectile dysfunction, and decreased libido with low free testosterone level. Statistically significant negative correlations were detected between calculated free testosterone and all of BMI, waist circumference, duration of diabetes, and HbA1c. Significant number of men with type 2 diabetes have low total and calculated free testosterone and inappropriate low or lower normal LH and FSH. There are inverse relationships between BMI and waist circumference with serum testosterone levels in men with type 2 diabetes.

1. INTRODUCTION

One-third of men with obesity or type 2 diabetes have subnormal free testosterone concentrations. The lower free testosterone concentrations are observed in obese men at all ages, including adolescents at completion of

puberty. The gonadotropin concentrations in these males are inappropriately normal; thus, these patients have hypogonadotropic hypogonadism (HH). The causative mechanism of diabetes and obesity induced HH is yet to be defined but is likely multifactorial. Decreased insulin and leptin signaling in the central nervous system are probably significant contributors. Contrary to popular belief, estrogen concentrations are lower in men with HH [1]. Hypogonadism is a medical term for decreased functional activity of the gonads. The gonads (ovaries or testes) produce hormones (testosterone, estradiol, anti-mullerian hormone, progesterone, inhibin B, and activing) and gametes (eggs or sperm). Male hypogonadism is characterized by a deficiency in testosterone – a critical hormone for sexual, cognitive, and body function and development [2]. Male hypogonadism should be diagnosed and treated, because when untreated, hypogonadal men may develop a clinical syndrome of decreased sexual function, infertility, fatigue, impaired sense of well-being, anemia, decreased bone density, decreased lean body mass (LBM) and muscle strength, as well as increased fat mass and visceral adiposity, which may be associated with metabolic dysfunction [3]. The decreased functional ability of the testis to produce adequate amounts of testosterone and/or mature spermatozoa can be due to defects in the testis, pituitary and/or hypothalamus, or at multiple levels [4]. Hypogonadism is often under-reported. According to some studies, 50% of men in their 80s are hypogonadal [5]. It has been estimated that hypogonadism currently affects up to 4 million American men, and as the population ages, this number will only rise. Nevertheless, only 5% of these men are being treated actively for hypogonadism. According to the most recent United States census, 13% of the population is above the age of 65 and this is expected to increase by 16% by 2020 [6]. Serum testosterone concentrations begin to increase with the onset of sleep and in young men, they peak at the first rapid eye movement sleep episode and remain at that level until waking. Testosterone production in men is related to rapid eye movement sleep, sleep duration, and sleep architecture [7]. Multiple studies have observed a negative correlation between testosterone levels and obesity, and several meta-analyses found that weight loss produces an increase in testosterone concentrations [8]. Studies have shown that free testosterone levels are low in obese men and correlates inversely with the degree of obesity. There is increased deposition of abdominal adipose tissue in hypogonadal patients, which in turn leads to a further decrease in testosterone concentrations, through conversion to estradiol by aromatase estradiol further favors abdominal fat deposition and perpetuates testosterone [9]. The aim of study to assess the relationship of hypogonadism with diabetes mellitus and obesity, based on both positive symptoms and low testosterone level in Iraqi men and identify what factors that may be associated with low serum testosterone level.

2. Method

This was a case control study that was conducted in the specialized center for endocrinology and diabetes in Baghdad – Al-Risafa and during a period of seven months from April until November 2019. The study included 200 patients and divided into two groups: case (type 2 DM) and control. Exclusion criteria: chronic liver or kidney diseases, infection or inflammation, medication with antiandrogen effect like finasteride, previously diagnosed with pubertal delay or infertility, anabolic steroids, Patients treated for prostate or breast problem. A questionnaire was applied to all enrolled study patients to collect the needed information. It was developed by the researcher (after thorough review of literatures) and revised by the supervisor. The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test (two tailed) was used to compare the continuous variables accordingly. Z-test was used to compare the categorical variables accordingly. Chi square test was used to assess the association between the calculated free testosterone level status and certain information. Pearson's correlation test (r) was used to assess correlation between continuous variables accordingly. A level of P – value less than 0.05 was considered significant.

3. Results

The total number of study participants was 200. They divided into two groups: Case group included 100 patients who were a known case of type 2 DM and control group included 100 participants who didn't have DM. The distribution of study groups by general characteristics is shown in figure and table (1). Study patients' age was ranging from 33 to 67 years old with a mean of 47.6 years and a standard deviation (SD) of ± 9.43 years. The highest proportion of study patients in case and control groups was aged between 40 – 59 years (53% and 49% respectively).

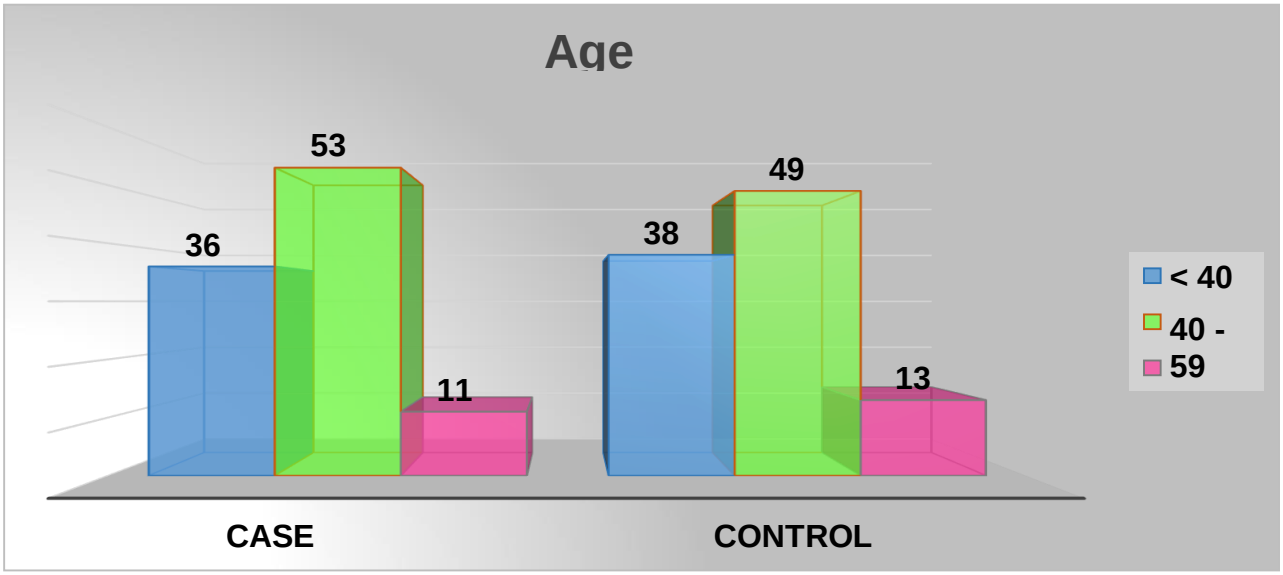

Figure 1: Distribution of study groups by age

The distribution of diabetic patients by certain clinical information is shown in table (3.2). We noticed that most of study patients (77%) were using oral drugs for treatment of diabetes. Regarding duration of diabetes, 45% of patients were diagnosed as diabetic for more than five years. About diabetes control, 81% of study patients were not well controlling their blood sugar (They showed HbA1c level ≥ 7%). The most common symptom was loss of energy (82%) followed by low mood (78%).

Table 1: Distribution of diabetic patients by certain clinical information:

Variable	No. (n=100)	Percentage (%)
Diabetes treatment		
Diet only	6	6.0
Insulin	17	17.0
Oral drugs	77	77.0
Duration of diabetes (Year)		
< 1	13	13.0
1 – 5	42	42.0
> 5	45	45.0
HbA1c level (%)		

< 7	19	19.0
≥ 7	81	81.0
Symptoms		
Loss of energy	82	82.0
Low mood	78	78.0
Erectile dysfunction	56	56.0
Decreased libido	41	41.0
Loss of hair	16	16.0

Figure 2 shows the comparison between study groups by means of LH, FSH, and total testosterone. Total testosterone level was low in 56% of case group compared to 19% in control group, and this difference was significant (P= 0.001). It was obvious that means of LH, and FSH were significantly lower in diabetic patients than that in controls (6.61 versus 9.32 U/l, P= 0.001; and 5.12 versus 10.25 U/l, P= 0.001 respectively).

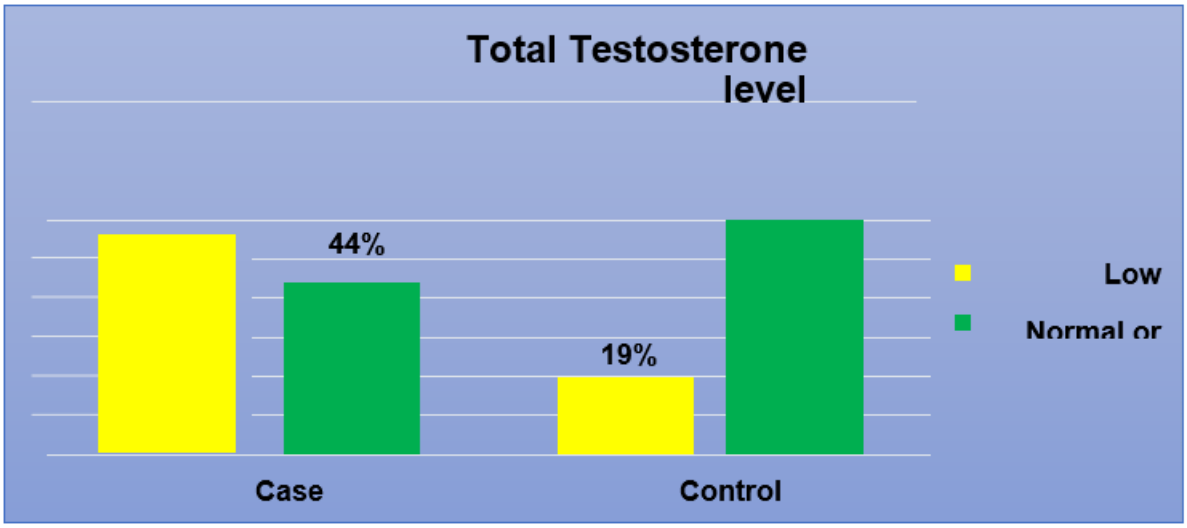

Figure 2: Total testosterone level in study groups

Table 2: Comparison between study groups by means of LH, FSH, and total testosterone

Variable		Study group		P - Value
		Case (n= 100) (%) or mean ± SD	Control (n= 100) (%) or mean ± SD	
Total Testosterone	Low	56%	19%	0.001
	Normal	44%	81%	
FSH (U/l)		5.12 ± 1.02	10.25 ± 3.4	0.001
LH (U/l)		6.61 ± 2.1	9.32 ± 3.1	0.001

Table 3 shows the association between calculated free testosterone level and general characteristics in diabetic patients. We noticed that the prevalence of low free testosterone level was significantly increasing with increasing in BMI level (58.1% of obese patients had low free testosterone level), P= 0.001. Regarding WC, 60.8% of patients who had high WC were showed low free testosterone level with a significant association (P= 0.001) between WC and calculated free testosterone level in diabetic patients. No statistical significant associations (P ≥ 0.05) between calculated free testosterone level in diabetic patients with age, smoking status, and hypertension.

Table 3: Association between calculated free testosterone level and general characteristics in diabetic patients

General characteristics	Calculated free testosterone level in diabetic patients		Total (%)	P - Value
	Low (%) n= 45	High/Normal (%) n= 55		
Age (Year)				
< 40	12 (33.3)	24 (66.7)	36 (36.0)	**0.144**
40 - 59	26 (49.1)	27 (50.9)	53 (53.0)	
≥ 60	7 (63.6)	4 (36.4)	11 (11.0)	
BMI Level				
Normal	5 (21.7)	18 (78.3)	23 (23.0)	**0.001**
Overweight	22 (47.8)	24 (52.2)	46 (46.0)	
Obese	18 (58.1)	13 (41.9)	31 (31.0)	
WC				
Normal	14 (28.6)	35 (71.4)	49 (49.0)	**0.001**
High	31 (60.8)	20 (39.2)	51 (51.0)	
Smoking status				
Non-smoker	20 (41.7)	28 (58.3)	48 (48.0)	**0.802**
Ex-smoker	6 (46.2)	7 (53.8)	13 (13.0)	
Current smoker	19 (48.7)	20 (51.3)	39 (39.0)	
Hypertension				
Yes	18 (47.4)	20 (52.6)	38 (38.0)	**0.709**
No	27 (43.5)	35 (56.5)	62 (62.0)	

Table 4 shows the association between calculated free testosterone level and certain clinical information of diabetic patients. We noticed that the prevalence of low free testosterone level was significantly increasing with increasing in duration of diabetes (55.6% of patients who had diabetes for more than five years had low free testosterone level), P= 0.034. Regarding HbA1c level, 50.6% of patients who had high HbA1c level showed low free testosterone level with a significant association (P= 0.019) between HbA1c level and calculated free testosterone level in diabetic patients. There were statistical significant associations between low mood (P= 0.031), erectile dysfunction (P= 0.029), and decreased libido (P= 0.023) with low free testosterone level. No statistical significant associations (P ≥ 0.05) between calculated free testosterone level in diabetic patients with type of diabetic treatment, loss of energy, and loss of hair.

Table 4: Association between calculated free testosterone level and certain clinical information of diabetic patients

Clinical information		Calculated free testosterone level in diabetic patients		Total (%)	P - Value
		Low (%) n= 45	High/Normal (%) n= 55		
Diabetes treatment					
Diet only		1 (16.7)	5 (83.3)	6 (6.0)	**0.203**
Insulin		6 (35.3)	11 (64.7)	17 (17.0)	
Oral drugs		38 (49.4)	39 (50.6)	77 (77.0)	
Duration of diabetes (Year)					
< 1		2 (15.4)	11 (84.6)	13 (13.0)	**0.034**
1 – 5		18 (42.9)	24 (57.1)	42 (42.0)	
> 5		25 (55.6)	20 (44.4)	45 (45.0)	
HbA1c level (%)					
< 7		4 (21.1)	15 (78.9)	19 (19.0)	**0.019**
≥ 7		41 (50.6)	40 (49.4)	81 (81.0)	
Symptoms					
Loss of energy	**Yes**	38 (46.3)	44 (53.7)	82 (82.0)	**0.564**
	No	7 (38.9)	11 (61.1)	18 (18.0)	
Low mood	**Yes**	38 (51.4)	36 (48.6)	74 (74.0)	**0.031**
	No	7 (26.9)	19 (73.1)	26 (26.0)	
Erectile dysfunction	**Yes**	34 (53.1)	30 (46.9)	64 (64.0)	**0.029**
	No	11 (30.6)	25 (69.4)	36 (36.0)	
Decreased libido	**Yes**	24 (58.5)	17 (41.5)	41 (41.0)	**0.023**
	No	21 (35.6)	38 (64.4)	59 (59.0)	
Loss of hair	**Yes**	6 (37.5)	10 (62.5)	16 (16.0)	**0.51**
	No	39 (46.4)	45 (53.6)	84 (84.0)	

4. Discussion

In the present study, total testosterone level was low in more than half (56%) of case group and this difference was significant (P= 0.001). It was obvious that means of LH, and FSH were significantly lower in diabetic patients than that in controls (6.61 versus 9.32 U/l, P= 0.001; and 5.12 versus 10.25 U/l, P= 0.001 respectively). By comparison to other studies, Al Hayek and colleagues in their study in 2017, that included 157 patients with type II diabetes mellitus, observed that in comparison with the normal patients, those with diabetes revealed significantly reduced level in the calculated bioavailable testosterone, as well as the free testosterone, LH, and SHBG. Compared with the normal patients, those with hypogonadism revealed significantly greater differences in the FSH levels (P<0.05) [10]. Another comparable results observed in [11] as noticed that hypogonadism occurred in 29.5% of the participants. Of them, 76.3% had serum FSH and or

LH that were either below or within the normal range and subjects with overt hypogonadism had significantly lower levels of both FSH (P = 0.002) and LH (P = 0.003) than their eugonadal counterparts. In this study, 45% of diabetic patients had hypogonadism in the form of low calculated free testosterone, while 55% showed normal or high calculated free testosterone. In comparison to other studies, results observed in Al Hayek et al study in 2017, in which 157 patients with type II diabetes mellitus enrolled. Results obtained showed that total frequency of hypogonadism was 22.9% of patients (36/157) (10), which was in concurrent to Agarwal et al study in 2017, as noticed that prevalence of hypogonadism was around 20.7% [12]. Another small results observed in Dhindsa et al study in 2010, in which levels of low testosterone was measured from 103 patients in the United States of America; the prevalence of hypogonadism observed was around 33% (13). In the present study, a statistically significant strong negative correlation was detected between calculated free testosterone and BMI (r= - 0.737, P= 0.001), statistically significant moderate negative correlation with WC (r= - 0.651, P= 0.001), significant strong negative correlation with duration of diabetes (r= - 0.793, P= 0.001) and finally, a significant weak negative correlation was detected between calculated free testosterone and HbA1c (r= - 0.182, P= 0.04). From the regression analysis done in Al Hayek et al study in 2017, BMI was isolated as an independent risk factor for hypogonadism. It is therefore evident that BMI is connected with a high incidence of hypogonadism and having diabetes augments that risk. Differently, regression analysis done in same study showed that type of diabetes treatment was not an independent risk factor for hypogonadism (10). On other hand, Dhindsa and others found in their study that conducted in 2010 on diabetic obese and lean male that Free testosterone concentrations were significantly ($P < 0.001$) and negatively related to age ($r = -0.38$), were significantly and negatively related to BMI ($r = -0.10$) and significantly and negatively related to SHBG ($r = -0.18$, $P < 0.001$), concluded that obesity is probably the condition most frequently associated with subnormal free testosterone concentrations in males [13].

5. Conclusion

Significant number of men with type 2 diabetes have low total and calculated free testosterone and inappropriate low or lower normal LH and FSH. There are inverse relationships between BMI and waist circumference with serum testosterone levels in men with type 2 diabetes. Symptomatic Hypogonadism is a common occurrence in men with type 2 diabetes particularly among those with low testosterone.

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