

PREVALENCE OF LOW FREE TESTOSTERONE LEVEL IN MEN WITH TYPE 2 DIABETES MELLITUS



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ABSTRACT

Background

Prevalence of low serum free testosterone levels in men with type2 diabetes mellitus has been reported worldwide.

Objectives

To find the prevalence of low free testosterone levels in type2 diabetic men.

Patients and Methods

A cross-sectional study was carried out in (the Diabetic and Endocrine Center) in Sulaimani from the 5th of April, 2017, to the 3rd of January, 2018. Eighty-eight male patients of type two diabetes mellitus who attended the centre for regular follow-up are included. After taking consent and history from the patient, a questionnaire was taken on Sociodemographic data and diabetic characteristics (duration & type of treatment), body mass index, and statin use. In addition, blood tests, including; free testosterone, were measured from morning samples using the ELISA kit (bioactive diagnostic, free testosterone ELISA kit), blood sugar (fasting), HbA1c, serum cholesterol, and serum triglyceride were done for all patients.

Results

There was little relation (correlation coefficient =0.07) (p-value 0.49) between free testosterone and HbA1c% concentration, and serum HbA1c% does not seem to contribute significantly to the free testosterone level variation. Duration of diabetes does not affect free testosterone levels.

Conclusion

The level of free testosterone in type2 diabetic men was average; there was no correlation between serum HbA1c concentration and serum-free testosterone.

Keywords: *Type2 diabetes mellitus, Serum-free testosterone level.*

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INTRODUCTION

Diabetes mellitus is a cluster of chronic metabolic conditions characterized by increased blood glucose levels caused by the body's inability to secrete insulin or resistance to insulin action, or both ⁽¹⁾.

In the tests, Leydig cells synthesize testosterone (T), which locally stimulates Sertoli cell function and spermatogenesis ⁽²⁾

The symptoms of testosterone deficiency include reduced libido and sexual dysfunction, decreased muscle mass and strength, more adiposity, depression, fatigue, osteoporosis, and bad life quality ⁽³⁾.

Hypertension, obesity, advanced age, diabetes, smoking, general health status, and physical inactivity are low testosterone risks ⁽⁴⁾.

Hypogonadism (HG), biochemical evidence of low testosterone, is linked with clinical symptoms, with or without signs ⁽⁵⁾.

The presence of HG and type2 diabetes mellitus (T2DM) increases with age. However, it is unclear whether HG contributes to type2 diabetes, whether type2 diabetes contributes to the development of HG, or whether the two are linked by an aging-associated condition such as obesity ⁽⁶⁾. Several recent studies have recorded a high prevalence of low free testosterone in type2 diabetic men ⁽⁷⁾.

Low serum T and sex hormone-binding globulin (SHBG) have been linked to metabolic syndrome, a cluster of clinical conditions including dyslipidemia, abdominal obesity, hypertension, and impaired glucose metabolism ⁽⁸⁾.

Decreased testosterone in diabetic patients is due to low levels of the SHBG due to insulin resistance and increased levels of inflammatory mediators, which may suppress the secretion of luteinizing hormone (LH) and gonadotropin-releasing hormone. Increased aromatase activity in visceral adipose tissue causes a conversion of T to Estradiol, leptin resistance causing lowered secretion of LH and testosterone ⁽⁹⁾.

Hypogonadotropic HG in type 2 diabetic patients has autoimmune pathogenesis, as indicated by ant pituitary antibodies at high titers, compared with age-matched control (10).

This study aimed to find the prevalence of low free testosterone levels in type2 diabetic men.

PATIENTS AND METHODS

The study started after the approval of the Iraqi Board Ethical Committee. A cross-sectional study was carried out at the Diabetes and Endocrine Center in Sulaimani from the 5th of April, 2017, to the 3rd of January, 2018.

A total of 88 cases of type two diabetes mellitus male patients presented to (the Diabetic and Endocrine) Center in Sulaimani for regular follow-up. Their age is between 35-80 years. The duration of diabetes is between 1-20 years. Most of them were on the oral anti-diabetic agent, some on insulin or a combination of insulin and oral anti-diabetic agent, while others were on a diet.

Exclusion criteria: Type 1 diabetes mellitus, patients with critical illness and multiple organ dysfunction, thyroid disease (hypothyroidism or hyperthyroidism), patients on steroid, anticonvulsant, and aldosterone antagonist, patients on steroid, anticonvulsant, and aldosterone antagonist.

The researcher attained the data through direct interviews and filling out a prepared questionnaire. The questionnaire includes the following; sociodemographic characteristics (age, residence, and history of smoking), duration of diabetes and type of treatment, use of statin or not, body mass index, blood sugar (fasting), free testosterone, fasting serum cholesterol & serum triglyceride (TG).

T2DM diagnosis was confirmed previously by a supervisor and physician in the (Diabetic and Endocrine Center

Serum-free testosterone tests were measured after taking blood samples in the morning and centrifuged; the samples were sent to the Central laboratory to complete the investigation. For laboratory measurements of free testosterone concentration, an enzyme immunoassay was applied for the quantitative determination of free testosterone (bioactive diagnostics, free testosterone ELISA kit).

Normal values

FT: 19-55 years: 1.00 – 28.28 pg/ml.

>55 years: 0.70 – 21.45 pg/ml (normal range of the Central lab).

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Statistical analyses were performed using SPSS-22, and descriptive analyses were performed as mean +_SD for continuous measures and absolute values (percentage) for categorical measures. In addition, person linear correlation was used to determine the association between free testosterone and HbA1c, and regression analysis was used to assess the contribution of other variables in the free testosterone. In all models, the significant level was defined as less than 0.05 for the p-value.

RESULTS

Free testosterone levels were measured from 88 types two diabetic men and correlated to the degree of glycemic control using HbA1c%. In addition, other patient characteristics like age, duration of diabetes mellitus, BMI, diabetic regimen, smoking habits, and different lab values for TG and Cholesterol were collected.

Mean Value for free testosterone, HbA1c %, and other continuous variables (Table 1).

The rate of testosterone adequacy, smoking, and use of Statins (Table 2).

A linear correlation technique was applied to

both variables to detect a correlation between free testosterone level and serum HbA1c percent. Then, the conclusion was that the correlation was negligible (correlation coefficient $r = 0.07$), and the P-value was (0.49), (Table 3). Regression analysis was used to test the strength of the relation between serum-free testosterone and HbA1c%. Unfortunately, the connection is so poor that the degree of HbA1C% control contributed only to 0.6% of the variation in testosterone level, which is negligible (p-Value (0.495), (Table 4).

Other variables of our study which might serve as probable predictors of free testosterone, namely (Age, BMI, Duration of Diabetes, S.TG, and S. Cholesterol), were put in a model for multiple regression analysis. However, again, none of these variables served as a strong predictor of free testosterone. These variables collectively contributed only to 1.9% of the variation among cases of serum-free testosterone, (Table 5).

Regarding statin intake among studied patients, 28 (31.8%) used statins, and 60 patients (68.2%) did not use statins. While the mean free testosterone was higher among statin users (10.95 ± 18.20 SD) Vs. (8.88 ± 5.56 SD), the P-Value for this difference is not significant, as seen in (Table 6).

Table 1. Mean Value for free testosterone, HbA1c % and other continuous variables.

	N	Minimum	Maximum	Mean	Std. Deviation
Age	88	35	80	55.95	9.31
Duration	88	1	20	6.40	4.92
BMI	88	19.50	50.00	29.93	4.54
HbA1c %	88	4.90	15.20	8.84	2.11
Free Testosterone	88	2.80	100.00	9.54	11.17
TG	88	40	925	210.09	149.59
Cholesterol	88	64.00	310.00	183.92	57.76

Table 2. Rate of testosterone adequacy, smoking, and use of Statins .

Testosterone Level for Age	Frequency	Percent
Normal	88	100%
Low	0	0%
Total	88	100%
Smoking		
Non-Smoker	35	39.8%
Smoker	20	22.7%
Ex-Smoker	33	37.5%
Total	88	100.0%
Statin Therapy		
No	60	68.2%
Yes	28	31.8%
Total	88	100.0%
Diabetic Regimes		
Diet	6	6.8%
Oral	69	78.4%
Insulin	4	4.5%
Combine	9	10.2%
Total	88	100.0%

Table 3. Correlations of free testosterone level and the level of HbA1c%.

Correlations	Free Testosterone	HbA1c%
Free Testosterone	Pearson Correlation	1
	P-value (2-tailed)	0.495
	N	88
HbA1c%	Pearson Correlation	0.07
	p-value (2-tailed)	0.495
	N	88

Table 4. The model is summary for regression analysis of HbA1c% as a predictor for free testosterone level.

Model Summary				
Model	R	R Square	Adjusted R Square	Std. The error in the Estimate
	.074a	.005	-0.006	11.20

^a Predictors: (Constant), HbA1c

Table 5. Multiple regression analysis of predictors of free testosterone level.

Predictors	Unstandardized Coefficients		Standardized Coefficients	p-Value
	B	Std. Error	Beta	
(Constant)	24.905	16.194		0.128
HbA1c	-.194	.646	-.037	0.764
Cholesterol	.020	.024	.103	0.414
TG	-.004	.009	-.056	0.634
BMI	-.223	.296	-.090	0.455
Duration	.474	.255	.209	0.067
Age	-.229	.139	-.191	0.104
Adjusted r2	0.019			

Table 6. Comparison of mean free testosterone level among statin and non-statin users.

Statin Use	Mean Free Testosterone	N	Std. Deviation	P-Value
No	8.88	60	5.56	
Yes	10.95	28	18.20	0.421
Total		88		

DISCUSSION

Male low testosterone is a global health problem ⁽¹³⁾. In addition, type two diabetes mellitus as a cause of low testosterone recently drew substantial attention ⁽¹⁴⁾.

This single-center experience study included eighty-eight patients with type two diabetes mellitus who attended the center for regular follow-up. Their level of testosterone (free) hormone was in normal ranges.

Our result is inconsistent with the Ho CH et al. ⁽¹⁵⁾ study among the population of Taiwan in 2015, in which 21.0% of cases have low serum testosterone (free) levels.

Another study by Rhoden El et al. ⁽¹⁶⁾ in Brazil found that 46% of 746 patients with type2 diabetes had low serum testosterone (free) levels.

Rezvani MR et al. ⁽¹⁷⁾ study among the Iranian population detected that Serum testosterone (free) concentrations were significantly decreased in type 2 diabetic men (2.53±1.68 pg/ml) than in healthy men (4.29±2.43 pg/ml) (P<0.001).

This disagreement between this study and other studies can be explained by its small sample size.

In our study, 22.7% of cases are smokers, and 37.5%

are X-smoker, and their testosterone levels are within the normal range.

Most cross-sectional studies have recorded a positive relationship between smoking and total or FT level ⁽¹⁸⁾.

Low testosterone level was found in men examined for idiopathic infertility after smoking cessation ⁽¹⁸⁾; it is unclear how smoking cessation reduces testosterone level ⁽¹⁹⁾. Multivariate analysis showed no link between total or FT levels and smoking, which agrees with previously published data ⁽²⁰⁾.

The disease duration of our diabetic patients ranges from (one year and twenty years) with a mean of 6.40, but the duration variable does not affect free testosterone level.

While the prevalence of LST was more in a patient having DM for a longer duration, multivariate analysis did not find any effect of duration variable on free testosterone level ⁽²¹⁾, which is consistent with our result.

Stanworth RD et al. ⁽²²⁾, in a study done in the United Kingdom in 2009, detected a link between statin use and low total testosterone, while bioavailable (free testosterone) was not lowered by statin use, which is consistent with our result.

Elderly patients have low testosterone (T) levels related to aging or other environmental factors such as minor illness, stress, and physical inactivity⁽²³⁾. However, the age of our participants does not affect test results, which may be due to the small sample size. Another study found no effect of age on testosterone levels⁽²⁴⁾. However, many studies found an association between LST and BMI in type 2 diabetic patients⁽²⁵⁾.

In contrast, a study found no association between T and BMI⁽²⁶⁾, which is consistent with our result. A study showed a strong relation between dyslipidemia and LS⁽³⁾, which is inconsistent with several other studies finding no significant association between them⁽²⁰⁾, similar to our research. Here HbA1c concentration has no effect on free testosterone in serum which is similar to some other studies^(3,27), while it is against the study of Kapoor et al.⁽²⁸⁾.

In conclusion, the free testosterone level in type2 diabetic men was normal; there was no correlation between serum HbA1c concentration and serum-free testosterone.

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