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Original Research Article

Estimation of serum testosterone concentration in type 2 diabetic males

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ABSTRACT

Background: A high incidence of hypogonadism in men with Type 2 Diabetes Mellitus has been globally reported. The present study was aimed at determining the frequency of hypogonadism in T2DM males. Screening and management of hypogonadism in Diabetic males should be done.
Methods: In this case control study conducted from January 2018 to August 2019 at SGRDIMSR Sri Amritsar 100 Type 2 Diabetic males were taken as cases. 50 age matched nondiabetic males were taken as controls. Apart from BMI and waist hip ratio routine investigations, HbA1C, serum total and free testosterone levels were done. All the subjects were subjected to ADAM questionnaire to evaluate for hypogonadism.
Results: Majority of subjects were in the age of 40-50 years. Mean Serum Total Testosterone levels in Study and Control Groups were 4.94±5.32 nmol/L and 6.63±4.54 nmol/L respectively (p=0.045). Mean Serum Free Testosterone levels in Study and Control Groups were 4.12±3.43 pg/ml and 6.05±3.24 pg/ml respectively (p=0.001). A statistically highly significant negative correlation was found between BMI and Serum Testosterone levels in both groups. Prevalence of hypogonadism (Total Testosterone <4.56 nmol/L) in Study and Control Groups was 73% and 58% respectively. Sensitivity and specificity of ADAM questionnaire was found to be 78.46% and 94.29 % respectively.
Conclusions: Prevalence of hypogonadism among T2DM males is high. So, screening for hypogonadism should be done. ADAM questionnaire can be used as a screening tool, results must be confirmed with Serum Total Testosterone levels.

Keywords: Hypogonadism, Total Testosterone, Type 2 Diabetes Mellitus

INTRODUCTION

Diabetes mellitus is fast becoming the epidemic of this century. Type-2 diabetes mellitus (T2DM), which is more in prevalence and the main driver of the epidemic, now affects 5.9% of the global population.[1] Hypogonadism is defined as a clinical syndrome which consists of clinical symptoms and associated with biochemical evidence of testosterone deficiency.[2] Male hypogonadism is a recognized medical condition that remains largely underdiagnosed.[3] Several large studies over the last few years have reported a high prevalence of low testosterone levels in men (hypogonadism) with T2DM.[4] Studies have also shown that testosterone levels are low in obese men and correlates inversely with the degree of obesity.[5]

Moreover, when combined with T2DM, obesity has been associated with a 50% prevalence of subnormal testosterone levels.[6]

METHODS

Among 100 Type 2 Diabetic males of more than 5 years duration were enrolled as cases and 50 age matched nondiabetic males were taken as controls. After the subjects fulfilled the inclusion and exclusion criteria, an informed consent was obtained from them before their final inclusion for participation in the study.

Inclusion criteria

- Known cases of Type 2 DM for more than 5 years
- Age of 30 years and above

Exclusion criteria

Following patients were excluded from the study

- Patients with known history of hypogonadism.
- Patients receiving exogenous testosterone.
- Patients suffering from cardiac disease, renal failure and liver cirrhosis.
- Patients suffering from AIDS.

After enrolling the subjects in the study, a thorough collateral history was taken, and a detailed clinical examination was done. Relevant investigations including the complete hemogram, renal and liver function tests, blood sugar levels and HBA1C were done in all subjects.

Apart from these investigations' serum total and free testosterone levels were also done in all the subjects. On the basis of low serum total testosterone levels (<4.56 nmol/L) the subjects were labelled as having hypogonadism. In addition, all the subjects were subjected to a 10 point ADAM questionnaire to evaluate for symptoms of hypogonadism.

The ADAM questionnaire includes ten questions

- Do you have a decrease in libido (sex drive)?
- Do you have a lack of energy?
- Do you have a decrease in strength and/or endurance?
- Have you lost height?
- Have you noticed a decreased 'enjoyment of life'?
- Are you sad and/or grumpy?
- Are your erections less strong?
- Have you noted a recent deterioration in your ability to play sports?
- Are you falling asleep after dinner?
- Has there been a recent deterioration in your work performance?

A subject is said to be having hypogonadism on the basis of ADAM questionnaire if either any 3 questions are responded positively or question number 1 and 7 are answered as 'Yes'. The results obtained from the study were statistically analysed using SPSS Statistics -19.0 version. The observations were tabulated in the form of mean±standard deviation (SD). The continuous variables were analysed using analysis of variance (ANOVA). In parametric data, student- t test was applied. Quantitative variables were correlated using chi-square test and coefficient of correlation. The data was analysed and level of significance was determined as its 'p' value with $p<0.05$ as significant, $p<0.001$ as highly significant and $p>0.05$ as non-significant.

RESULTS

In the present study subjects enrolled were of the age 30 years and above. The majority of the subjects in Study Group were in the age group 40-50 years (n=34, 34%) and majority of the subjects in Control Group were also in the same age group (n=19, 38%). The mean age for subjects in Study Group was 50.92±8.35 years and that in Control Group was 49.20±9.39 years. Both the groups were matched for age (p value = 0.276).

In the Study Group 64% patients had diabetes for 5-10 years, 27% patients had diabetes for 10-15 years, 5% patients had diabetes for 15-20 years and 4% patients had diabetes for >20 years. Mean duration of diabetes in study group was 8.45±4.34 years.

In the Study Group 53% patients were found to be hypertensive whereas in the control group 42% subjects had hypertension as defined by JNC-8 guidelines. Mean systolic and diastolic blood pressure in Study Group was 137.84±18.65 mmHg and 85.48±11.19 mmHg respectively. Mean systolic and diastolic blood pressure in Control Group was 127.12±15.84 mmHg and 81.04±10.60 mmHg respectively. The difference in both systolic and diastolic blood pressure of two groups was statistically significant (p value=0.001 and 0.021 respectively).

BMI was calculated in all the subjects and the subjects were divided on the basis of BMI range, mean BMI was calculated and compared in two groups as it is depicted in (Table 1). 8% of patients in Study Group and 2% of subjects in Control Group had BMI < 17.5 kg/m^2. 27% of patients in Study Group and 60% of subjects in Control Group had BMI between (17.5-22.9 kg/m^2). 63% of patients in Study Group and 36% subjects in Control Group had BMI between (23-29.9 kg/m^2). 2% of patients in Study Group and 2% of subjects in Control Group had BMI > 30 kg/m^2. Mean BMI of subjects in Study and Control Group was 24.48±2.63 kg/m^2 and 22.09±2.25 kg/m2 respectively and the difference was highly statistically significant (p value = 0.000) (Table 1)

Mean HbA1C in the Study and Control Groups was found to be 9.52±2.11 % and 5.35±0.61 % respectively. The difference was highly statistically significant (p value 0.000). Mean waist hip ratio in Study Group was found to be 0.91±0.05 whereas it was 0.88±0.04 in the Control Group. The difference was statistically significant (p value = 0.019).

Subjects in two groups were divided on the basis serum total testosterone levels, mean value in both the groups was calculated and compared, as it is depicted in Table No. 2. 65% patients in Study Group and 40% subjects in Control Group had serum total testosterone levels between 0.00-4.50 nmol/L. 15% patients in Study Group and 34% subjects in Control Group had serum total testosterone levels between 4.50-9.00 nmol/L. 11% patients in Study Group and 20% subjects in Control Group had serum total testosterone levels between 9.0-13.50 nmol/L. 7% patients in Study Group and 4% subjects in Control Group had serum total testosterone levels between 13.50-18.00 nmol/L. 7% patients in Study Group and 4% subjects in Control Group had serum total testosterone levels between 13.50-18.00 nmol/L. 2% subjects each in Study and Control Group had serum total testosterone levels more than 22.50 nmol/L. Mean serum total testosterone levels in Study Group were found to be 4.94±5.32 nmol/L which were significantly lower than mean serum total testosterone levels in Control Group i.e. 6.63±4.54 nmol/L (p value = 0.045) (Table 2).

Table 1: Distribution of subjects on the basis of BMI in 2 groups.

BMI (Kg/m^2)	Study Group		Control Group	
	No. of patients (n)	Percentage (%)	No. of Subjects (n)	Percentage (%)
<17.5	8	8.0	1	2.0
17.5-22.9	27	27.0	30	60.0
23-29.9	63	63.0	18	36.0
>30	2	2.0	1	2.0
Total	100	100.0	50	100.0
Mean±SD	24.48±2.63		22.09±2.25	
p value	0.000			

Subjects in both the groups were divided on the basis of serum free testosterone levels, mean value was calculated in both the groups and compared as it has been depicted in (Table 3). 62% patients in Study Group and 46% subjects in Control Group had serum free testosterone levels between 0.00–5.00 pg/ml. 30% patients in Study Group and 46% subjects in Control Group had serum free testosterone levels between 5.00-10.00 pg/ml. 7% patients in Study Group and 6% subjects in Control Group had serum free testosterone levels between 10.00-15.00 pg/ml. 1% patients in Study Group and 2% subjects in Control Group had serum free testosterone levels between 15.00-20.00 pg/ml. Mean serum free testosterone levels in Study Group were found to be 4.12±3.43 pg/ml which were significantly lower than that in Control Group i.e. 6.05±3.24 pg/ml (p value = 0.001) (Table 3). A highly significant negative correlation was observed between Body Mass Index (BMI) and Serum Total Testosterone Levels in Study Group (r = -0.645, p value < 0.001) by using Pearson's correlation. With increase in BMI, Serum Total Testosterone Levels declined as shown in (Figure 1). A highly significant negative correlation was observed between Body Mass Index (BMI) and Serum Free Testosterone Levels in Study Group (r = -0.567, p value < 0.001) by using Pearson's correlation. With increase in BMI, Serum Free Testosterone Levels declined as shown in (Figure 2).

Table 2: distribution of subjects on the basis of serum total testosterone levels in 2 groups (normal = 4.56-28.2nmol/l).

Serum Total Testosterone Levels (Normal = 4.56-28.2 nmol/L)	Study Group		Control Group	
	No. of patients (n)	Percentage (%)	No. of Subjects (n)	Percentage (%)
0.00 - 4.50	65	65.0	20	40.0
4.50 - 9.00	15	15.0	17	34.0
9.00 -13.50	11	11.0	10	20.0
13.50-18.00	7	7.0	2	4.0
18.00-22.50	0	0.0	0	0.0
22.50-27.00	1	1.0	1	2.0
27.00 and Above	1	1.0	0	0.0
Total	100	100.0	50	100.0
Mean±SD	4.94±5.32		6.63±4.54	
p Value	0.045			

Table 3: Distribution of subjects on the basis of serum free testosterone levels (normal = 5 to 30 pg/ml).

Serum Free Testosterone Levels (Normal = 5 to 30 pg/ml)	Study Group		Control Group	
	No. of Patients (n)	Percentage (%)	No. of Subjects (n)	Percentage (%)
0.00 - 5.00	62	62.0	23	46.0
5.00 -10.00	30	30.0	23	46.0
0.00 -15.00	7	7.0	3	6.0
15.00-20.00	1	1.0	1	2.0
20.00 and Above	0	0.0	0	0.0
Total	100	100.0	50	100.0
Mean	4.12±3.43		6.05±3.24	
p Value	0.001			

Table 4: Characteristics of ADAM questionnaire.

	True Positive	False Positive	True Negative	False Negative	n	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Accuracy (%)
Cases	51	2	33	14	100	78.46	94.29	96.23	70.21	84.00
Controls	9	2	28	11	50	45.00	93.33	81.82	71.79	74.00

A significant negative correlation was observed between Body Mass Index (BMI) and Serum Total Testosterone Levels in Control Group (r = -0.284, p value = 0.045) by using Pearson's correlation. With increase in BMI, Serum Total Testosterone Levels declined as shown in (Figure 3)

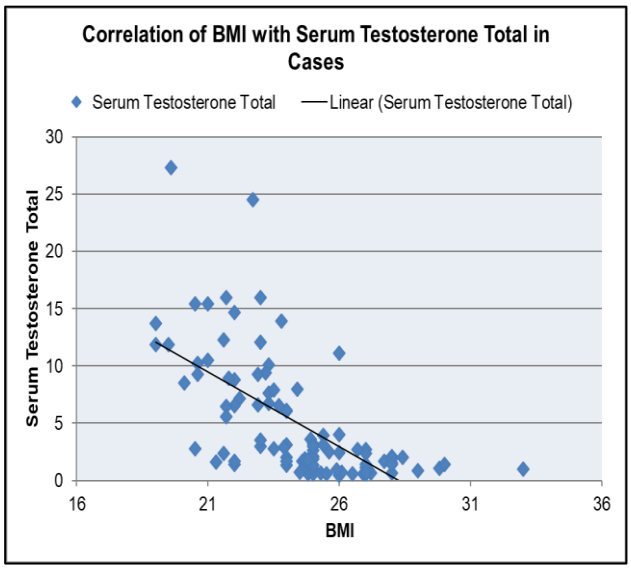

Figure 1: Negative correlation between Body Mass Index and serum total testosterone levels in study group.

A significant negative correlation was observed between Body Mass Index (BMI) and Serum Free Testosterone Levels in Control Group (r = -0.311, p value = 0.028) by using Pearson's correlation. With increase in BMI, Serum Free Testosterone Levels declined as shown in (Figure 4).

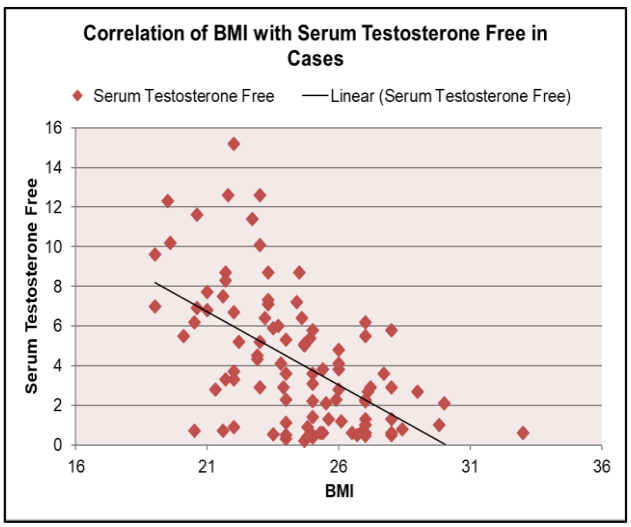

Figure 2: Negative correlation between Body Mass Index and serum free testosterone levels in study group.

In the present study no correlation was observed between duration of Type 2 DM and Serum Testosterone levels (Both Total and Free). No correlation was observed between HBA1C values and serum testosterone levels (Both Total and Free).

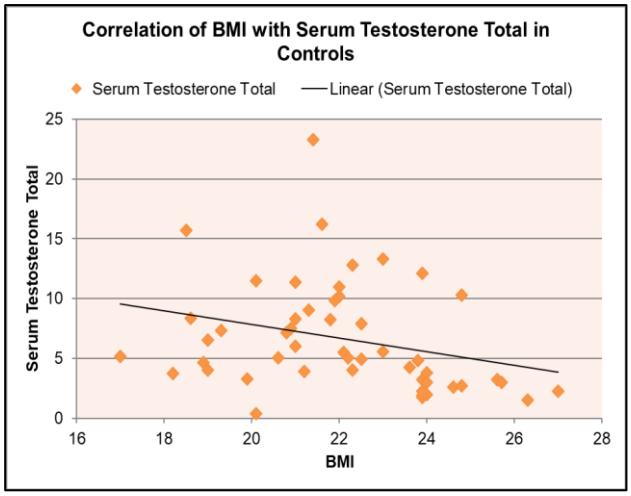

Figure 3: Negative correlation between Body Mass Index (BMI) and serum total testosterone Levels in control group.

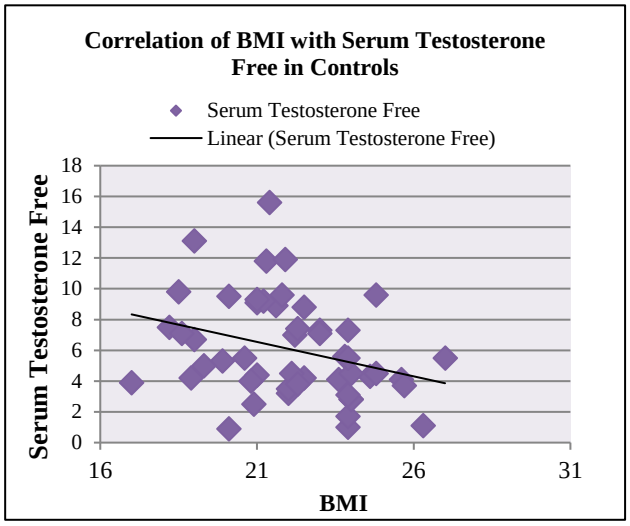

Figure 4: Negative correlation between Body Mass Index (BMI) and serum free testosterone levels in control group.

On the basis of Serum Total Testosterone levels (<4.56 nmol/L) the prevalence of hypogonadism was found to be 65% in Study Group and 40% in Control Group and this difference was found to be statistically significant (p value = 0.004). On the basis of ADAM questionnaire, the prevalence of hypogonadism was found to be 53% in Study Group and 22% in Control Group and this difference was found to be statistically significant (p value = 0.001). True positives, false positives, true negatives and false negatives in both the groups were calculated and are tabulated in (Table 4). On the basis of this data sensitivity, specificity, positive and negative predictive values of ADAM questionnaire were calculated. In the Study Group sensitivity of ADAM questionnaire was found to be 78.46%, specificity 94.29%, positive predictive value 96.23%, negative predictive value 70.21% and an accuracy of 84.00%. In the Control Group sensitivity of ADAM questionnaire was found to be 45.00%, specificity 93.33%, positive predictive value 81.82%, negative predictive value 71.79% and an accuracy of 84.00% as shown in (Table 4).

DISCUSSION

Hypogonadism is defined as a clinical syndrome which consists of clinical symptoms and associated with biochemical evidence of testosterone deficiency. Recently, the association between hypogonadism and T2DM has been demonstrated in numerous studies.

In the present study, majority of the subjects in each group were between the age of 40–50 years. 34% patients in the Study Group and 38% subjects in Control Group were in the age group of 40-50 years. The mean age of patients in Study Group was 50.92±8.35 years and of subjects in Control Group was 49.20±9.39 years. The two groups were matched for age.

In the present study, the percentage of hypertensive subjects in Study Group was found to be 53% whereas it was found to be 42% in the Control Group. Mean systolic and diastolic blood pressure in Study Group were 137.84±18.65 mmHg and 85.48±11.19 mmHg respectively whereas mean systolic and diastolic blood pressure in Control Group were 127.12±15.84 mmHg and 81.04±10.60 mmHg respectively. In a study done by Kaleab Tadesse et al, more than half (55%) of the type 2 diabetic patients were found to be hypertensive according to JNC 8 criteria. The mean Systolic and Diastolic blood pressure of study subjects among type 2 Diabetes Mellitus patients were 135.98±17.[11] and 88.89±12.77 mmHg respectively in their study.[7] The results of this study are consistent with their study.

In this study majority of the patients in Study Group 63% had BMI between 23-29.9 kg/m^2 whereas in Control Group most of the subjects 60% (n = 30) had BMI in the range of 17.5-22.9 kg/m^2 The mean BMI in the study group was found to be 24.48±2.63 kg/m2 and in the control group it came out to be 22.09±2.25 kg/m^2. There were more obese patients in Study Group and the difference was statistically significant (p value < 0.001). Sandeep Singh et al, in their case control study showed that the body mass index (BMI) of the study subjects (diabetics) was 23.94±1.83 kg/m^2 and that of controls was 22.8±1.38 kg/m^2 (p<0.001).[8] The results are comparable to this study.

In the present study 65% patients in Study Group and 40% subjects in Control Group had serum total testosterone levels between 0.00-4.50 nmol/L. 15% patients in Study Group and 34% subjects in Control Group had serum total testosterone levels between 4.50-9.00 nmol/L. 11% patients in Study Group and 20% subjects in Control Group had serum total testosterone levels between 9.00-13.50 nmol/L. 7% patients in Study Group and 4% subjects in Control Group had serum total testosterone levels between 13.50-18.00 nmol/L. 7%

patients in Study Group and 4% subjects in Control Group had serum total testosterone levels between 13.50-18.00 nmol/L. 2% subjects each in Study and Control Group had serum total testosterone levels more than 22.50 nmol/L. Mean serum total testosterone levels in Study Group were found to be 4.94±5.32 nmol/L which were significantly lower than mean serum total testosterone levels in Control Group i.e. 6.63±4.54 nmol/L (p value = 0.045). Results are similar to a study conducted by Jyoti Trivedi et al, which concluded that serum total testosterone levels in diabetic group (i.e. 3.53±1.38 ng/ml) were significantly lower than that in nondiabetic control group (5.81±2.42ng/ml) (p-value<0.001).[9]

Among 62% patients in Study Group and 46% subjects in Control Group had serum free testosterone levels between 0.00–5.00 pg/ml. 30% patients in Study Group and 46% subjects in Control Group had serum free testosterone levels between 5.00-10.00 pg/ml. 7% patients in Study Group and 6% subjects in Control Group had serum free testosterone levels between 10.00-15.00 pg/ml. 1% patients in Study Group and 2% subjects in Control Group had serum free testosterone levels between 15.00-20.00 pg/ml. Mean serum free testosterone levels in Study Group were found to be 4.12±3.43 pg/ml which were significantly lower than that in Control Group i.e. 6.05±3.24 pg/ml (p value = 0.001). The study by Satish Chaudhary et al. also determined serum total and free testosterone levels in type 2 diabetes mellitus male patients and concluded that type 2 diabetes mellitus is associated with low levels of total and free testosterone.[10]

In Study Group a statistically highly significant negative correlation was observed between BMI and Serum Total Testosterone levels (Correlation Coefficient = -0.645, p value <0.001) and, between BMI and serum Free Testosterone levels (Correlation Coefficient = -0.567, p value <0.001). Similar were the findings of the study conducted by Ayman Abdullah Al Hayek et al.[11] and Kapoor D et al.[12]

In the present study prevalence of hypogonadism (Serum Total Testosterone Levels < 4.56 nmol/L) was found to be 65% in diabetic males. In a study conducted by S.V. Madhu et al, Hypogonadism was observed in 40% diabetic males with coronary artery disease and 32% diabetic males without coronary artery disease.[13] In another study conducted by Dhindsa et al. involving 103 patients in the United States of America, the prevalence was found to be around 33%.[4]

In this study sensitivity and specificity of ADAM questionnaire in Study Group was found to be 78.46% and 94.29% respectively. These results are different from study conducted by Theophilus E Ugwu et al, in which ADAM questionnaire was found to have a sensitivity of 88.1% and a specificity of 44.7 %.[14] In this study no correlation was observed between duration of Type 2 DM and serum testosterone levels. These findings are similar to the findings of a study conducted by Jyoti Trivedi et al. which concluded that serum testosterone concentration might be independent of the duration of T2DM.[9]

In this study no correlation was observed between HBA1C values and serum testosterone levels. Similar were the results of a study conducted by Rendong Zheng et al.[15]

CONCLUSION

This study suggests that there is high prevalence of hypogonadism in T2DM males. Serum testosterone levels in T2DM males tend to be significantly lower as compared to their nondiabetic counterparts. Further, deranged BMI is a risk factor for low levels of serum testosterone. So, while managing Type 2 Diabetes male patients screening for hypogonadism should be done. Although ADAM questionnaire can be used as a screening tool, the results must be confirmed with biochemical levels of Serum Total Testosterone and where needed testosterone replacement should be considered.

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