A Study on Free Testosterone Level in Type 2 Diabetes

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Abstract
Introduction:
The predominant form of Diabetes worldwide is Type 2 Diabetes mellitus and its pathophysiology is much known to us.Testosterone is known to be the Sex hormone for males.Testosterone is needed for general health, well being and sexual function in men.Many studies have stated that the testosterone might have a role in development of metabolic disorders like Diabetes mellitus.

Aim:
The aim of the study was to evaluate the serum levels of free testosterone in type 2 Diabetes mellitus.

Methodology:
The study was done in the Department of Medicine, Assam Medical College, Dibrugarh Which is a tertiary care centre from June 2020 to May 2021.The sample size was calculated based on Mattack N et al study whose standard deviation was 0.258 nmol/L, with 95% confidence interval and with true value ±5 and the final sample size attained as 110. All patients with type 2 Diabetes Mellitus having the symptoms of androgen deficiency were included in the study. Patients with documented hypogonadism, Hormone replacement therapy treatment, Acute illness history, Chronic kidney and liver disease, suffering from HIV, taking drugs which interfere with the testosterone level and not willing to participate were excluded. The data was entered in the MS word and analysis done with SPSS 23. P value <0.05 was considered as significant.

Results:
The mean age of the study participants was found to be 46.13±10.22 and majority belonged to 40-49 years of age.The serum testosterone range across all age group was found to be 5-39pg/ml. There was a definite decrease in the serum free testosterone level among the diabetic patients with every 10 years increase in age and it was found to be statistically significant (p value <0.001). There was a statistically significant (p value =0.022) decrease in the serum free testosterone level with increase in the duration of diabetes.A significant negative corelation (r value: -0.5713, p value<0.001) was observed between serum free testosterone and glycated haemoglobin level in male type 2 diabetic patients.

Conclusion:
Early detection of low serum free testosterone levels and its replacement helps achieve optimum control of the glycemic status and improves the overall quality of life of diabetes patients.

Keywords: Type 2 Diabetes mellitus, Free Testosterone, Glycemic status, Hypogonadism, HbA1c

Introduction

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances in carbohydrate,fat and protein metabolism which results from insulin

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secretion defects,action of insulin or both.When fully manifested diabetes is characterized by hyperglycemia but it can be detected early by presence of glucose intolerance.It is considered as one of the major public health issue which is more commonly affecting from 20-79 years of age and around 463 million affected people living world wide.It was estimated that in 2030 around 578 million people affected with diabetes will be all around as its prevalence keeps on increasing.

Indian Council of Medical Research stated that India has 62.4 million and 77.2 million people with diabetes and prediabetes respectively(1).90% of the diabetic population is suffering from Type 2 Diabetes Mellitus(T2DM).Diabetes Mellitus is found to be associated with both microvascular and macrovascular complications such as cardiovascular diseases,peripheral neuropathy,infection,stroke,renal failure and retinopathy etc.

Not only treatment but prevention is also very essential in diabetes.This disease occurs due to disproportion between the insulin level and the insulin sensitivity which results in functional deficit of insulin.Chronic hyperglycemia leads to nonenzymatic glycation of proteins and lipids the extent of which can be measured by the glycation hemoglobin (HbA1C) test.These glycated products leads to complications like retinopathy,nephropathy and neuropathy(2)

Resistance to insulin is multifactorial but usually develops from obesity and aging(3).The treatment of diabetes is purely a multidisciplinary approach like lifestyle modifications,oral hypoglycemic drugs ,insulin therapy,regular foot care and other supportive measures.Certain studies proposed that testosterone deficiency was possibly linked with few systemic illness.T2DM is one such systemic illness.Many studies suggested that low serum testosterone is associated with obesity, metabolic syndrome and hyperglycemia.Testosterone plays a major role in the metabolism of glucose and lipids.Thus low levels of serum testosterone can lead to altered metabolic profile.

A high prevalence of hypogonadism in men with type 2 diabetes mellitus is seen in multiple studies. Hence this study was done to evaluate the level of free testosterone in type 2 diabetes mellitus patients in the north eastern part of India.

Methodology:

Study setting:

Hospital based cross sectional study was conducted in the Department of Medicine,Assam Medical College,Dibrugarh which is a tertiary care centre.The study was done for a period of one year ,from June 2020 to May 2021.

Sample Size:

The sample size was attained based on Mattack N et al(4) study. The Standard deviation of serum Free Testosterone level among the diabetic patients was 0.258nmol/L, and considering 95% confidence interval with true value as ± 5%, the sample size calculated was 107 and was rounded off to 110.

Inclusion Criteria:

All patients of type 2 Diabetes Mellitus with symptoms of androgen deficiency attending the Medicine department of Assam Medical College and within the age group of 18 to 65 years were included.

Exclusion Criteria:

Patients with documented hypogonadism,Hormone replacement therapy treatment,Acute illness history,Chronic kidney and liver disease,suffering from HIV,taking drugs which interfere with the testosterone level and not willing to participate were excluded.

Data Collection:

After obtaining the informed written consent, all the study subjects were evaluated by thorough clinical history, physical examination, and appropriate investigations.

The following parameters were documented in the study proforma.

1. Personal particulars like Name, Age, Gender, occupation, Present, and Past History,response to ADAM questionnaire were documented. General and systemic examination was done, vitals recorded, the outcome was documented.

2. Hematological and biochemical investigations, Routine blood examination,Renal function test,serum electrolytes,fasting blood sugar,HbA1C,Urine

routine,Fasting lipid levels and serum free testosterone levels were done.

Statistical analysis:

After collecting the data,it was entered in MS excel Windows10.Statistical analysis was done in SPSS 21.Continuous data were expressed in terms of Mean±Standard deviation and compared by independet sample t test.Categorical variable were expressed in terms of numbers(percentages) and compared by the chi-square test.Pearson's correlation coefficient(r) was used to measure the associations among continuous variables.For all analyses,P value of <0.05 was considered as significant.

Results:

Table1:Baseline characteristics of the study participants with serum free testosterone:

Baseline features	Mean±Standard deviation	P value
Age Group(in years)	FreeTestosterone (pg/ml)	
20-29	33.84±4.19	<0.001
30-39	25.39±5.36	
40-49	23.35±5.34	
50-59	21.83±5.25	
>=60	17.64±4	
Duration(in years)		
<=5	24.79±6.74	0.02
6-10	23.20±5.45	
11-15	21.50±3.44	
>15	17.82±7.21	
Total Cholesterol		
<200	26.66±4.56	<0.001
200-240	21.09±4.16	
>240	16.46±5.74	

The decrease in the serum free testosterone level among the diabetic patients was significant. Similarly mean difference between the duration of the disease and the total cholesterol with the serum free testosterone was found to be statistically significant.

Table 2:Laboratory parameters of the study participants:

Parameters	Mean±SD
Hemoglobin (gm %)	11.56±1.89
Total count (Cells/mm^3)	7843.64±2153.59
Platelet(Lakh cells/mm^3)	2.20±0.21

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Urea (mg/dl)	29.55±10.10
Creatinine(mg/dl)	0.80±0.31
Sodium (mmol/l)	136.07±5.79
Potassium (mmol/l)	4.14±0.51
Fasting blood sugar(mg/dl)	210.27±53.03
Total cholesterol (mg/dl)	192.59±47.29
HbA1c(%)	8.75 ±1.66
Serum Free testosterone (pg/ml)	23.21±5.98

In the laboratory parameters the mean Hemoglobin level was 11.56±1.89 .The mean total count and platelet count was 7843.64±2153.59 and 2.20±0.21.The renal function test results of the study participants like mean creatinine value was 0.80±0.31 and that of the mean urea was 29.55±10.10.

The serum electrolytes values of Sodium was 136.07±5.79 and that of potassium was 4.14±0.51.

The fasting blood sugar level was 210.27±53.03 and the total cholesterol level was 192.59±47.29.The HbA1c mean was found to be 8.75±1.66 and the mean serum free testosterone was 23.21±5.98.

Table 3:Correlation of the parameters with the serum free testosterone

Characteristics	r value (Pearson's)	P value
Age	-0.5096	<0.001
Fasting blood sugar	-0.8375	<0.001
Total cholesterol	-0.7074	<0.001
HbA1c	-0.5713	<0.001

A Pearson correlation was done to find out the correlation between the age,fasting blood sugar level,total cholesterol and HbA1c with that of the serum testosterone.A highly significant negative correlation was found between all the variables like Age,Fasting blood sugar,Total cholesterol and HbA1c with Serum testosterone.Fasting blood sugar and Total cholesterol were found to have strong negative correlation (FBS—0.8375,Total cholesterol-0.7074) whereas the Age and the HbA1c found to have moderate negative correlation.

Discussion:

The present study was a hospital based observational cross sectional study done in Assam Medical College and Hospital,Dibrugarh among 110 type 2 Diabetes mellitus patients with symptoms of hypogonadism.In our study majority of the study participants 33.64% belonged to 40-49 years of age category and the

mean age of the study participants was found to be 46.13±10.22 years.Similar results was also found in Trivedi and Kapoor et al(5) study where the mean age was found to be 46.20±7.17 years.Similar mean age was also found in studies done by Agarwal et al(6) ,Viswanathan et al(7) ,Eva et al(8) and European male ageing study(9).

Among the age group of 20-29 years free testosterone level was found to be 28-39 pg/ml,in 30-39 years of age 11-38 pg/ml,in 40-49 years 9-32pg/ml,in 50-59 years 5-31pg/ml and in 60-65 years of age 6-23 pg/ml. This decrease in serum free testosterone was statistically significant(p value<0.001).Similar results was also seen in Ramachandran S et al (10) study which also showed lower level of free testosterone in type 2 Diabetes mellitus patients.Tint AN et al(11) also portrayed similar results where, as the age increases the free testosterone level decreases in type 2 DM.Dhindsa et al(12) also showed similar results with total testosterone level and free testosterone level in his study.

In present study subjects with duration of diabetes mellitus within 5 years and 6-10 years were of 38.18% and 18.18% were having T2DM for 11-15 years of age and 5.45% for >15 years.The mean duration of type 2 Diabetes mellitus was 7.76±4.42 years.Similar mean duration was also observed in studies done by Dhinsda S et al(12) where the mean duration was 7.7±0.7 years.Hayek AA et al(13) also showed similar results in their study.

The mean free testosterone level according to duration of diabetes in the study subjects were as follows: 24.79±6.74pg/ml in <=5 years duration,23.20±5.45pg/ml in 6-10 years duration,21.50±3.44pg/ml which was in 11-15 years duration and for >15 years duration it was 17.82±7.21pg/ml.A decrease in free testosterone level was seen with increase in the duration of diabetes and it was found to be statistically significant(p value 0.022).Similar results was also seen in Hayak AA et al (13)study.But it was in contrast with the study done by Ganesh HK et al(14) where there was no significant correlation between the free testosterone and duration of diabetes mellitus.

Subjects in our study with total cholesterol value <200 mg/dl wa 50.91%, in 200-240 mg/dl was of 33.64% and >240 mg/dl was 15.45%.The mean serum cholesterol was 192.59±47.29 mg /dl.Similar

results were also seen in Mattack N et al(4) where the mean serum cholesterol was found to be 193.50±48.99 mg/dl.

The mean serum free testosterone level according to the total cholesterol level were found to be 26.66±4.56pg/dl for <200 mg/dl and 21.09±4.16 pg/dl for cholesterol 200-240 mg/dl and 16.46±5.74 pg/dl for cholesterol >240 mg/dl and was found to be statistically significant, ie.,with increase in cholesterol level there was a statistically significant(p value <0.001) decrease in the serum free testosterone.Similar results was also seen in Yassin et al(15),Mattack N et al(4) and in Cheung et al(16) studies.

Negative Correlation was found to be statistically significant(p value <0.05) with variables like age,Fasting blood sugar ,Total cholesterol and HbA1C.Thus there was a decrease in serum free testosterone with increase in variables like age,Fasting blood sugar,Total cholesterol and HbA1c.Many studies supported this findings(12)(13)(4)(15)(17)(18)(19).

Limitation:

The main limitations of the study were small sample size,lack of standardization of free testosterone measurements methods and unavailability of harmonized reference ranges for free testosterone.Also as the study was a cross sectional study we could not make out whether diabetes preceded or followed the decline in free testosterone level.

Conclusion:

It can be concluded from our study that majority of the male with type 2 diabetes mellitus have significant reduction in free testosterone levels. Significant negative correlation was found between glycated haemoglobin and serum free testosterone level. Thus it can be summarised from our study that male type 2 diabetes patients have low free testosterone and lower the serum testosterone level poorer is the glycemic status. Serum free testosterone variations can also be used as a biomarker to assess the progression of type 2 diabetes mellitus.So earlier we dectect the low serum free testosterone levels, sooner we can replace it in the type 2 diabetes patients and it helps us achieve a better glycemic

control and also can improve the quality of life of diabetes patients**.**

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