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A retrospective correlative study on serum testosterone level and type-2 diabetes

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Abstract
Introduction: Testosterone is a hormone that plays a key role in male health and development. However, it is also linked to diabetes, a metabolic disorder affecting many individuals all over the world. Those with diabetes have an increased chance of developing low testosterone levels, while those with low testosterone levels may be at a higher risk of developing diabetes.
Aim and Objective: Present study was conducted to find the link between testosterone and diabetes in order to determine whether low testosterone levels can lead to diabetes.
Materials and Methods: The study was conducted in men, who were diagnosed as type 2 diabetes mellitus patients and confirmed by the estimation of FBS, PPBS, and HbA1C. Healthy age and BMI matched individuals, were selected as controls. The laboratory investigations included evaluation of serum testosterone levels and creatinine was carried out by standard method.
Result and Discussion: The results showed that low testosterone levels in men could be linked to an increased risk of developing type 2 diabetes. The exact mechanism behind this is still unknown, but it appears to be a result of the testosterone's ability to affect glucose metabolism. Low testosterone levels can lead to a decrease in insulin sensitivity, which can eventually lead to diabetes.
Conclusion: Overall, it appears that there is a link between testosterone and diabetes, with low testosterone levels in men potentially leading to an increased risk of developing diabetes. It is important to maintain healthy testosterone levels in order to reduce the risk of diabetes.

Keywords: Testosterone, type 2 diabetes, hypogonadism, HbA1C

Introduction
Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hypoglycemia, factors may include reduced insulin secretion, and decreased glucose utilization and increase glucose production depending upon the etiology of DM. Metabolic dysreglation associated with DM causes secondary pathophysiologic changes in multiple organ systems. DM is the most common endocrine disease about 8% of the total population and about 20% of persons above the age of 50 suffer from this disease [1]. The chronic hyperglycemia of DM is associated with long term damage, dysfunction and failure of various organs like kidneys, eyes, heart, nerves and blood vessels. Untreated diabetes can cause many complications. Acute complication includes diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include heart disease, stroke, kidney failure, foot ulcers and damage to the eyes.
Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. In the early state of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improves insulin sensitivity or reduce glucose production by the lines. Type 2 diabetes is due to lifestyle factors and genetics. A number of life style factors are known to be impatient to the development of type 2 diabetes, including obesity, lack of physical activity, poor diet, stress and urbanization [2].
Testosterone is the principle sex hormone responsible for the development of reproductive function in male vertebrates. As a blood hormone, testosterone is derived from cholesterol. The majority of the hormone is secreted from the testes, hence the term testosterone. If is also secreted in small amounts by the adrenal gland and by the ovaries in females, males

secrete about ten times more testosterone than females. Testosterone acts as a key facilitator in the growth and development of males and is responsible for the development of the male reproductive organs such as the testes, penis and prostate Also promotes secondary sexual characteristics during puberty. In adult males, levels of testosterone are about 7-8 times as great as in adult females, but as the metabolic consumption of testosterone in males is greater, the daily production is about 20 times greater in men [3].

Testosterone helps the body's tissues take up more blood sugar in response to insulin. Men with low testosterone more often have insulin resistance: they need to produce more insulin to keep blood sugar normal. As many as half of men with diabetes have low testosterone, when randomly tested. Scientists aren't sure whether diabetes causes low testosterone, or the other way around. Hence the purpose of the present study was to find out the relation between type 2 diabetes mellitus and serum testosterone level in male patients.

Materials and Methods

A retrospective study was conducted at MES Medical college hospital, 650 bedded multispecialty hospital, Perinthalmanna. Being a retrospective study, the data of 20 Type 2 diabetic male patients and 20 healthy individuals related to the specific purpose were made available from the MRD of the hospital under strict control and supervision.

Inclusion criteria

Men above 18 years who were diagnosed as type 2 diabetes mellitus were considered as the test population and DM was confirmed by the estimation of fasting blood sugar level (≥126mg/dl), post prandial blood sugar level (≥200mg/dl) and HbA1C (≥6.5%). Men matched with BMI having the normal FBS, PPBS, and HbA1C were selected as the control population.

Exclusion criteria

Patients with a known history of hypogonadism, panhypopituitarism, hyperthyroidism, patients taking exogenous testosterone and glucocorticoids, patients suffering from chronic debilitating disease, such as renal failure, cardiac failure, liver cirrhosis, or HIV, were excluded from the study.

Study design

Information on demographic data, personal history and history of present illness, and other co-morbid conditions were collected followed by the clinical and systematic examination of all the patients. The laboratory investigations included evaluation of serum testosterone levels, blood glucose levels (fasting blood glucose and postprandial plasma glucose), with the levels of HbA1c and creatinine was done with the standerd procedure. The 5-10 ml venous sample was obtained after an overnight fast of 8-12 hours under aseptic conditions. Centrifugation of the blood was done at 4000 rpm for 5 minutes for separation of plasma. Analysis of FBS was done on fresh plasma. 4-5 ml of blood sample was allowed to clot and then centrifuged at 200 rpm for 10 min. Then the clear serum was separated and were transferred into sample cups. Serum concentration of testosterone was measured by ARCHITECT testosterone assay based on the principle Chemiluminescent Microparticle Immunoassay (CMIA) by using kits provided by ARCHITECT; 1000 SR. Remaining serum was frozen at -30 ℃, used for estimation of serum creatinine levels. Two millilitre of whole blood was collected in Ethylene-diamine tetra acetic acid (EDTA) containers for analysis of HbA1c. The mean level of serum testosterone was calculated in various age and BMI groups and compared with controls.

Statistical analysis

Statistical analysis was performed using SPSS 20.0. Results on continuous and categorical measurements are represented as mean ± SD and number (%). Pearson's correlation test was performed to measure the linear dependence of the study parameters. Significance between the study parameters was determined by Chi-square/Fisher exact test and student t-test. $p<0.05$ is considered statistically significant.

Results

The study has not reported a significant differences in mean age between groups (P= 0.629). The mean age of control group was found to be 40.63±5.42 years and that of the test group was found as 41.45±6.24 years. The BMI in test group was 26.11±2.4 kg/m2, which was higher as compared to the standard group with a value of 24.03±2.34 kg/m2 (p-value= 0.05). The FBS and PPBS level in test group was found to be 148±14 mg/dl and 172±18 mg/dl respectively, which was significantly higher (93±6 and 124 ±8 respectively) in control group when compared to the test group. A significant difference (p-value <0.056) was observed in the HbA1c value of test group (08.12±1.62 %) when compared to the standard group (4.92±0.43 %). The level of Serum creatinine in diabetic group was 1.20±0.52 mg/dl, which was found significantly higher than control group with serum total creatinine level 0.99±0.26 mg/dl, (p-value = 0.0024). The level of serum total testosterone of diabetic group was 4.39±1.02 ng/ml, which was found significantly lower than control group with serum total testosterone level 5.98±1.86 ng/ml, (p-value < 0.0001).

Table 1: Comparison of various parameters between study groups

Parameters	Control	Case
Age	40.63±5.42	41.45±6.24 (P= 0.629)
BMI	24.03±2.34	26.11±2.43 (p-value= 0.056)
FBS (mg/dl)	93±6	148±14** (p-value <0.05)
PPBS (mg/dl)	124 ±8	172±18** (p-value <0.05)
HBA1C (%)	4.92±0.43	08.12±1.62**(p-value <0.05)
Serum Creatinine (mg/dl)	0.99±0.26	1.20±0.52 (p-value = 0.0032).
Total Testosterone (ng/ml)	5.98±1.86	4.39±1.02*** (p-value < 0.0001)

Table 2: Comparison of testosterone values indifferent age groups

Age group	Testosterone level (ng/ml)	
	Control group	Test group
25 – 35 yrs old	7.99	5.55** (p-value <0.05)
36 – 45 yrs old	5.92	4.72** (p-value <0.05)
46 – 55 yrs old	3.69	2.90** (p-value <0.05)

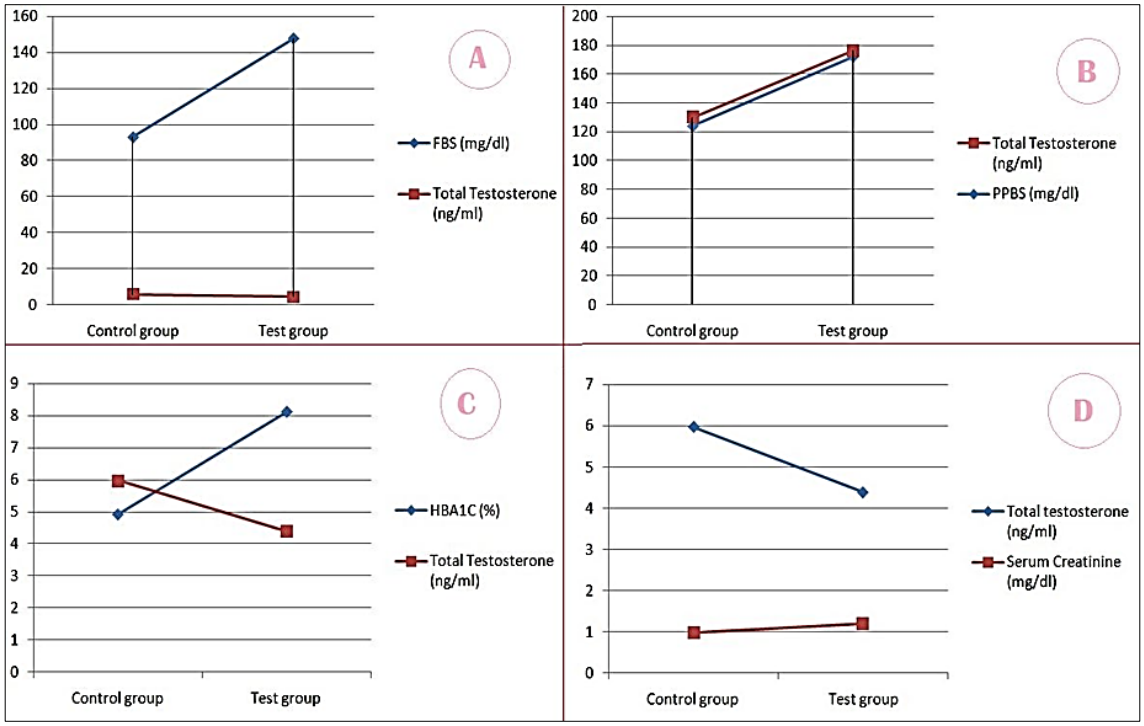

Fig 1: A- Comparison of FBS level and serum testosterone level in test and control group, B- Comparison of PPBS level and serum testosterone level in test and control group, C- Comparison of HbA1C level and serum testosterone level in test and control group, D- Comparison of serum creatinine level and serum testosterone level in test and control group

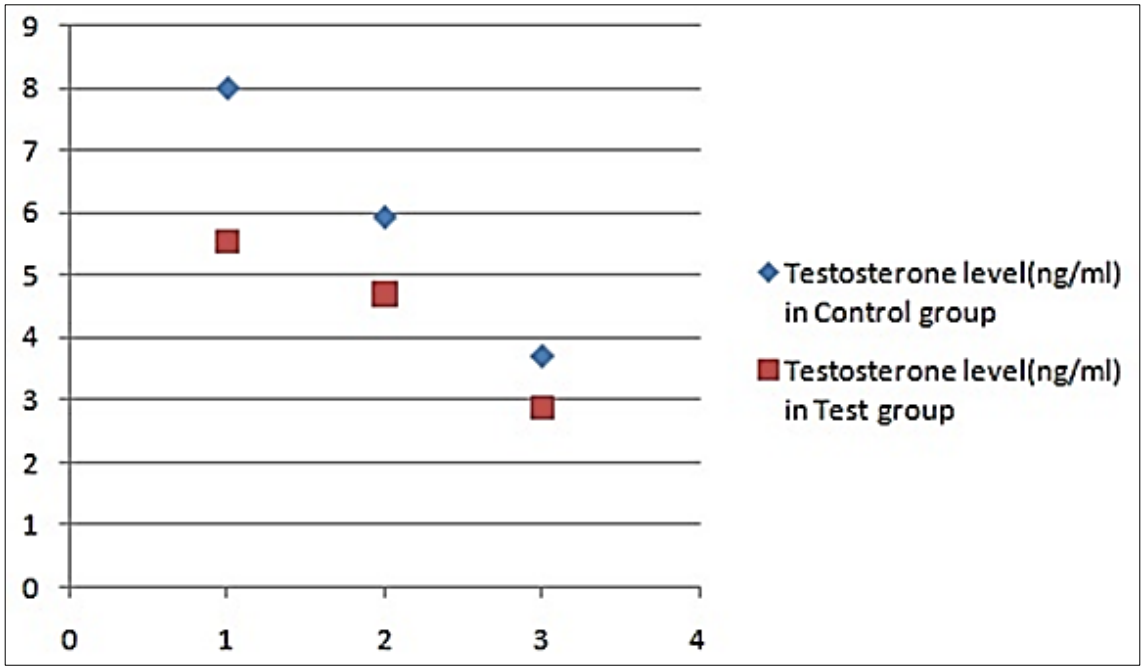

Fig 2: Comparison of testosterone values indifferent age groups

As to evaluate the serum testosterone level in different age groups of type 2 diabetic male patients, they are classified into different groups and a graph was plotted according to the data collected. From the result it can be seen that as the age increases the level of serum testosterone is markedly reduced in both control and test group.

Discussion

Testosterone is a sex hormone that regulates a number of processes in the human body, including fertility, sex drive, bone mass, fat distribution, muscle mass, and red blood cell production. Testosterone levels typically decrease as age increases, but for some people, these levels can become too low and cause unwanted symptoms. Diabetes is a condition in which the body is unable to process blood glucose, also known as blood sugar. The present study was undertaken to evaluate the relation between type 2 diabetes mellitus and serum testosterone level in male patients. From the data shown on the table 1, it has been observed that the male patients who were suffering from type – 2 diabetes mellitus had reduced serum testosterone level, indicates the significant associate of hypogonadism. From the result it is clear that the normal individuals have testosterone levels only between the normal limit but in case of type 2 diabetes male patients it is seen to be reduced up to 3.97 mg/ml. There are several mechanisms for the association of low

serum testosterone level and type-2 diabetes with insulin resistance and obesity as central features. In experimental studies, androgen receptor knockout mice developed significant insulin resistance rapidly [4]. These findings explained the well-known effects of testosterone therapy on body composition in men including increment in muscle mass and reduction in fat mass, both of which were expected to decrease insulin resistance [5]. Besides, microarray studies in mice showed that testosterone regulated skeletal muscle genes involved in glucose metabolism that led to decreased systemic insulin resistance [6]. In the liver, hepatic androgen receptor signaling inhibited development of insulin resistance in mice [7]. Thus, by promoting lipolysis and myogenesis, testosterone might lead to improved insulin resistance.

Most recently, a higher level of testosterone was shown to independently predict a reduced risk of type 2 diabetes in elderly men [8]. Whereas a lower level was an independent risk factor for high fasting glucose [9]. A study by Hackett [10]. Assessed the use of testosterone replacement therapy (TRT) in men with type 2 diabetes and low testosterone. The study found that taking TRT improved blood sugar control, insulin resistance, cholesterol levels, and visceral fat. Likewise, a more recent study in 356 men with type 2 diabetes and low testosterone found that long-term treatment with TRT improved both glycemic control and insulin resistance [11]. Androgen improves insulin resistance by changing body composition and reducing body fat. Although a low serum testosterone level could contribute to the development of obesity and type 2 diabetes through changes in body composition, obesity might also alter the metabolism of testosterone. In obese men, the peripheral conversion from testosterone to estrogen could attenuate the amplitude of luteinizing hormone pulses and centrally inhibit testosterone production to exacerbate the vicious cycle of obesity and low serum testosterone level [9]. In brief, multiple lines of evidence from animal experiments, observational studies and randomized controlled trials in humans all appeared to implicate the possible causal role of low serum testosterone level in type 2 diabetes and obesity, although larger-scale randomized clinical studies are required.

Testosterone levels are at their highest during adolescence and early adulthood. As men get older, testosterone levels may decline about 1% a year after age 30 [12]. This can lead to a variety of changes such as reduced sex drive. While lower testosterone levels may be concerning, it's a natural part of aging. Testosterone biosynthesis by Leydig cells within the testis occurs in response to luteinizing hormone, which is secreted by the pituitary. Once LH binds to the LH receptors on the Leydig cell, there is the rapid synthesis may take place. Leydig cells are less responsive to gonadotropin stimulation in elderly males as compared to younger males [13]. Rubens and colleagues demonstrated the decreased responsiveness of Leydig cells in older men by stimulating males with human chorionic gonadotropin (HCG) and measuring the increases in serum levels of T [13]. In addition to the diminishing responsiveness of Leydig cells to LH as men age, Neaves and colleagues using cadaveric tissue demonstrated that older men have a decreased numbers of Leydig cells compared to younger men. Taken together, the mechanism of primary hypogonadism in aging men may be a combination of decreased number of leydig cells, acquired defects in the steroidogenic pathway, as well as a disruption of the regulatory systems within the cells [14].

Development of T2DM may lead to low testosterone levels, testosterone replacement therapy could help to fight against diabetes. A study in 2015 reports that, 24 weeks of TRT saw a dramatic increase in their insulin sensitivity levels in the study population [15].

Conclusion

From the present study, it is concluded that the level of serum testosterone in type 2 diabetic male patients is reduced. Serum testosterone level in type 2 diabetic male patients is reduced according to their age. In conclusion, the relationship between testosterone and diabetes is complex and multifaceted. Low testosterone levels in men have been linked to an increased risk of developing diabetes, while high testosterone levels can also have negative effects on glucose metabolism and insulin sensitivity. Further research is needed to fully understand the impact of testosterone on diabetes and to determine the best approach for managing these conditions.

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