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Evaluation of Serum Testosterone Level in Men with Type 2 Diabetes Mellitus

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Abstract
Background: *Levels of testosterone and presence of anemia in diabetic males has been in focus over the past decade. Correlation of the testosterone level with anemia in such patients can help in improved diagnosis and management of diabetic condition.*
Aim: *The present study was conducted to estimate the serum testosterone levels and correlate it with hematocrit levels in type 2 diabetes patients.*
Methodology: *A total of 150 men were selected and divided into diabetic (HbA1c ≥ 6.5 %; n = 75) and non-diabetic (HbA1c ≤ 6.5 %, n= 75) groups, after diagnosis for the case-control study conducted for a period of 1 year. Serum levels of creatinine, ferritin, and iron were evaluated along with blood sugar and hematocrit levels. Serum testosterone levels were analyzed by enzyme-linked immunosorbent assay. Pearson's correlation test, Chi square test, and student t-test were used for statistical analysis.P<0.05 was considered statistically significant.*
Results: *Testosterone levels were significantly (P< 0.001) correlated with hematocrit levels, body mass index, blood sugar levels, fasting blood sugar levels and postprandial plasma sugar levels. Serum iron levels (82.80 ± 38.09 vs. 93.77 ± 26.7µg/dL; P = 0.043) were significantly reduced in the diabetic patients with low testosterone level (187.42 ± 145.01 vs.406.91 ± 135.55 ng/dL; P = 0.0001). In contrast, serum ferritin level was more in diabetic group (P = 0.0023).*
Conclusion: *Reduced testosterone level can be used to determine insulin resistance and anemia and therefore can be further assessed for its establishment as a marker for the same.*
Keywords: *Hematocrit, Anemia, HbA1c, blood sugar*

Introduction

Sexual dysfunction is one of the most frequent consequence of DM, especially in men with a prevalence of 25-30%[1]. Hypogonadism is among the most common causes of sexual dysfunction and its incidence in type 2 diabetes in men has been increased in the recent times[1,2].

Hypogonadism develops due to reduced production of sex hormones such as testosterone and leads to diminished gonadal activity [3].Reduced testosterone, especially with the advancement in age gives rise to symptoms such as loss of libido, mood changes, reduced strength and tiredness [4].

Low levels of testosterone has been associated with the development of insulin resistance and reduction in hematocrit and hemoglobin levels leading to anemic condition[4]. The reduction in hematocrit levels is due to the lack of stimulating effect on erythropoietin, which otherwise leads to an increase in the production of the red blood cells [5]. Studies on effect of serum testosterone on biochemical factors has been currently in focus due to its role in the development of several diseases (osteoporosis, diabetes, anemia, amongst others). The evaluation of serum testosterone in diabetic patients include the analysis of HbA1c levels. However, the correlation studies between the levels of serum testosterone and HbA1c have been contrasting in nature[6,7]. Therefore, the present study was conducted to analyze the correlation between the levels of hematocrit and serum testosterone in the type II diabetic patients.

Materials and Methodology

This 1-year case–control study was conducted from January 2015 to December 2015.Ethical clearance was obtained from the Institutional Ethics Committee.

A total of 150men with fasting blood sugar level ≥126 mg/dL, postprandial plasma sugar level ≥200 mg/Dl and HbA1c of ≥6.5% were selected for the study. Patients under glucocorticoid therapy or who were diagnosed with acute renal failure, cirrhosis orhuman immunodeficiency virus infection were excluded from the study. Patients were divided into diabetic (n = 75) and nondiabetic (n = 75) groups based on HbA1c levels. Patients having HbA1c ≥ 6.5 % were included in diabetic group and patients with HbA1c ≤6.5 % included in nondiabetic group. Written consent was obtained from the patients before the commencement of the study.

Information on demographic data, personal history and history of present illness, and other comorbid conditions were collected followed by the clinical and systematic examination of all the patients. The laboratory investigations included evaluation of hemoglobin, hematocrit levels, serum testosterone levels, blood sugar levels (fasting blood sugar and postprandial plasma sugar), serum iron and ferritin levels, and total ion binding capacity along with the levels of HbA1c and creatinine. Patients in the diabetic group were also evaluated for paleness of the skin and the type (insulin or oral hypoglycemic agent) and duration of treatment—regular or irregular treatment. Levels of fatigue and alterations in libido were also noted in the diabetic patients. Enzyme-linked immunosorbent assay was used to evaluate the serum testosterone levels in the studied groups[8].

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 association between mean ages in both the groups was not significant ($P= 0.22$; Table 1). In the diabetic group, the association between the insulin and oral hypoglycemic agent treatments was highly significant ($P = 0.0001$). Results showed that 58.67% of patients were on insulin and 41.33%were on oral hypoglycemic agents. In addition, 49.33% of the patients were on regular treatment; however, 50.67% patients were on irregular mode of treatment.

Examination of pallor in the patients of both the groups revealed unhealthy pale appearance in 26.67% and 22.67% of patients in diabetic and non diabetic group, respectively. Upon evaluation of the peripheral blood smear, patients in both the groups were diagnosed with normocytic normo-chromic anemia (66.66% and 77.33% in diabetic and nondiabetic groups, respectively), microcytic hypochromic (33.33 % and 21.33% in diabetic and nondiabetic groups, respectively), and dimorphic anemia (1.33% in nondiabetic group).

Evaluation of clinical features of hypogonadism and its correlation with testosterone and hematocrit in the diabetic group revealed low testosterone and low hematocrit levels in 72% and 28% of patients, respectively. Among 72% of patients with low testosterone levels, decreased libido and fatigue was observed in 25.92% and 14.81% of patients, respectively. Of the 28% of patients with low hematocrit, 28.57 % and 9.52% patients were observed to have decreased libido and fatigue, respectively. Comparison of various biochemical parameters in diabetics and nondiabetic group revealed a significant association among the levels of testosterone, fasting blood sugar, postprandial plasma sugar, serum iron, total iron binding capacity, HbA1c, and creatinine (Table 1).

Evaluation of hematocrit levels in the diabetic group revealed that 72% of patients had hematocrit level within 40-50%; however, 26.6% of patients had <40% hematocrit level. In addition, the serum testosterone level in the diabetic group was <241ng/dL in 73.33% of patients, whereas remaining 26.66% of patients had serum testosterone level between 241 and 827 ng/dL.

Highly significant correlation was observed between serum testosterone level and biochemical parameters (Table 2).Positive correlation was observed between serum testosterone level and hematocrit values (r = 0.454; P = 0.000042). In contrast, negative correlation was observed between serum testosterone levels and biochemical parameters such as BMI (r = −0.3669; P = 0.0012), HbA1c (r = −0.3648; P = 0.0013), fasting blood sugar (r = −0.431; P = 0.0001), and postprandial plasma sugar(r = −0.4234; P = 0.0002).

Table 1. Comparison of study parameters between diabetic and non diabetic groups

Variables	Diabetic patients (n = 75)	Non-diabetic patients (n = 75)	*P*-value
Age (years)	55.75 ± 8.98	55.95 ± 10.13	0.22
Body mass index (BMI; kg/m^2)	24.15± 2.44	23.72 ± 2.11	0.244
Hemoglobin (g/dl)	11.94 ± 1.78	12.20 ± 1.75	0.370
Hematocrit (%)	41.81 ± 4.26	42.92 ± 3.07	0.068
Testosterone (ng/dL)	187.42 ± 145.01	406.91 ± 135.55	0.0001
Fasting blood sugar (mg/dL)	187.15 ± 66.06	84.27 ± 13.59	0.0001
Postprandial blood sugar (mg/dL)	268.91 ± 86.91	129.63 ± 14.96	0.0001
Serum iron(µg/dL)	82.80 ± 38.09	93.77 ± 26.7	0.0430
Total iron binding capacity (µg/dL)	330.19 ± 94.02	299.96 ± 86.48	0.0422
Serum ferritin(ng/mL)	113.35 ± 87.02	102.63 ± 52.74	0.363
HbA1c (%)	9.64 ± 2.28	4.48 ± 0.77	0.0001
Creatinine (mg/dL)	1.29 ± 0.75	1.00 ± 0.28	0.0023

Table 2: Correlation of testosterone level with biochemical parameters

Variables	HbA1c	Hematocrit	Fasting blood sugar (mg/dL)	Postprandial plasma sugar (mg/dL)	BMI (kg/m^2)
Testosterone (ng/dL)	−0.3648**	0.4541**	−0.4314**	−0.4234**	−0.3669**

Discussion

Reduced testosterone levels with the advancement in age has been associated with anemia, fatigue and decreased libido along with increased risk of cardiovascular problems, depression and atherosclerosis [9]. The present study demonstrated reduced testosterone levels in majority of the diabetic patients (72%) along with reduced hematocrit levels leading to development of typical symptoms of hypogonadism such as decreased libido and enhanced fatigue condition. Fatigue condition can also be due to the development of anemic conditions including normocytic normochromic, microcytic hypochromic and dimorphic anemia, as observed in the present study[10]. In general, geriatric populations

with low level of testosterone have been found to be at a higher risk of anemia [11].

The present study also demonstrated decrease in hematocrit level in the diabetic patients, which may possibly due to the presence of anemic condition [10]. Similar results were obtained in the 41.33% of the diabetic patients of the present study exhibiting reduced serum iron level. Since iron is vital to produce red blood cells, the reduced iron levels may increase susceptibility of hypogonadism patients to anemia[12]. Such observations indicate that reduced testosterone levels leads to reduction in red blood cells resulting in anemic condition [13]. On the other hand, high ferritin levels during the time of puberty often act as a risk factor leading to the development of hypogonadism, as suggested by Shalitin et al[14]. In addition, with the progression of age, decrease in testosterone level may lead to reduction in iron level, thereby increasing the risk of anemia in men. Thus, administration of the testosterone can help in the increasing libido and treat macrocytic and microcytic anemia by enhancing the absorption of iron from intestine and process of erythropoiesis activation leading to increase in the hemoglobin levels [15].

Serum testosterone treatments have also been reported to impact the HbA1c levels in diabetic patients [16]. Several contrary reports have been published with respect to the correlation between serum testosterone and HbA1c levels. Dhindsa et al.,[17] Grossmn et al.,[18] and Ayman et al.[19] reported no significant correlation between HbA1c and testosterone levels, which is in contrast with those by Kapoor et al[20]. in which testosterone level correlated positively with HbA1c level. On the other hand, a study on Japanese men revealed negative association between testosterone level and HbA1c, possibly due to decrease in stimulatory effect of testosterone on red blood synthesis [21]. However, the present study demonstrated negative correlation between the serum testosterone and HbA1c levels, possibly indicating reduction in HbA1c levels in diabetic patients with administration of testosterone.

Low levels of testosterone has been reported to be associated with type II diabetes and insulin resistance along with inappropriately low levels of hematocrit values [19,22,23]. The decrease in hormone level is slow and constant over all decades and starts early in life, probably after the third or fourth decade. The exact cause of the age-related reduction in testosterone levels is not known. Evaluation of fasting blood sugar and postprandial plasma sugar levels in normal and diabetic patients in the present study revealed significantly higher blood sugar levels in the diabetic patients. The correlation between the blood sugar level and serum testosterone was found to be significant and negatively correlated, indicating improvement in blood sugar levels with increase in serum testosterone. Studies have reported inverse relationship between blood sugar and testosterone[24]. The treatment of hypogonadism by means of testosterone replacement therapy often leads to reduction in blood sugar level along with reduction in the resistance to insulin among the diabetic patients [22, 25].

Present study revealed significant correlation between BMI and serum testosterone. Testosterone level was reduced in diabetic patients with increased BMI. Similar results were reported by Aftab et al.[26] and Dhindsa et al.[17], demonstrating significant association between BMI and low serum testosterone level.

In conclusion, low testosterone level can be one of the predictive marker for determining insulin resistance, anemia and, other metabolic conditions. Testosterone administration may; however, help in treating the conditions by decreasing resistance to insulin, increasing iron absorption, and reducing BMI. Further research with a considerably larger population and other clinical parameters may aid in establishing testosterone level as a marker in early diagnosis and treatment.

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