ORIGINAL ARTICLE
TESTOSTERONE LEVELS IN PATIENTS OF ERECTILE DYSFUNCTION WITH AND WITHOUT TYPE 2 DIABETES MELLITUS

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Background: There is strong association of erectile dysfunction with age and level of testosterone. The objective of the present study was estimation and comparison of testosterone levels in erectile dysfunction (ED) patients with/without type 2 diabetes mellitus (T2DM). **Methods:** A comparative cross-sectional study conducted at Khyber Teaching Hospital and Government Naseerullah Babar Memorial Hospital, Peshawar. Male patients of ED, aged 30 to 65 years, with or without diabetes mellitus, were included in the study. Patients with active co-morbidities and unmarried patients were excluded. Assessment of serum testosterone levels (total and free) was done in all subjects. Data was analyzed using SPSS-23. Mean and Standard Deviation were calculated. Independent sample *t*-test was performed for comparison between the two groups. The severity of ED was assessed using SHIM score. **Results:** Majority of patients were 40–49 years old (44.5%). Duration of erectile dysfunction was higher in diabetic patients compared to non-diabetics. The total testosterone in serum of diabetics with ED was 493.09±24.9 ng/dL, and 499.53±23.83 in non-diabetic ED patients. Free testosterone was significantly low in diabetic group (*p*<0.05). Free testosterone was significantly lower in diabetic patients of our study as compared to the non-diabetic ED patients (59.07 pg/ml *vs* 68.25 pg/ml respectively), (*p*=0.049). **Conclusion:** There was no significant difference between the testosterone levels of the two groups. However, free testosterone was significantly reduced in type 2 diabetics compared to non-diabetics with ED.
Keywords: Testosterone, Erectile dysfunction, ED, Diabetes mellitus, T2DM

INTRODUCTION

There is strong association of erectile dysfunction with increasing age and decrease in the levels of testosterone. A lot of researches observed the effects of deficiency of male hormones on sexual performance mainly by inhibiting the production or action of male hormones.[1] It has been observed that testosterone directly causes relaxation of penile smooth muscles through release of nitric oxide (NO), RHO-associated protein kinase (ROCK), phosphodiesterase-5 (PDE5) and the adrenergic response.[2,3]

The total and free testosterone levels are reportedly not related to the level of sexual desire in men with erectile dysfunction.[4] When erectile dysfunction is severe, it is probable that free testosterone levels are below the normal limit.[5] Free testosterone level is decreased with increasing age. As the age increases, the serum hormone binding globulin (SHBG) also increases, so that free testosterone is more likely to bind with SHBG, resulting in further decrease of free testosterone in the serum.[6] About 20% of diabetic patients are suffering from hypogonadism and approximately 50% of patients have low free testosterone levels than the guidelines of European Association of Urology.[7]

The relation between diabetes and low testosterone level is poorly understood. Cohen suggested that decrease insulin activity increases peripheral aromatase function in adipose tissues that converts free testosterone to estradiol. This leads to further decrease in serum testosterone level.[8] Decrease in the level of testosterone leads to increase in lipoprotein lipase activity which indirectly enhances the uptake of free fatty acids by adipose tissue promoting the obesity. This ultimately leads to leptin hormone resistance in the body causing energy disturbance, i.e., promotes further fat storage in adipocytes. Leptin resistance reduces release of luteinizing hormone and testosterone.[9]

Patients with Type-2 Diabetes Mellitus are three times more likely to develop erectile dysfunction.[10] The longer duration of diabetes is strongly associated with ED.[11,12] The increased blood glucose level is strongly associated with a higher risk of erectile dysfunction.[13,14]

Men with erectile dysfunction have 75% increased risk of developing peripheral vascular disease.[15] It is said that men resist psychological explanation for erectile dysfunction, but counselling can be effective.[16] SHIM score is used for grading erectile dysfunction. Erectile dysfunction is associated with serious health co-morbidities like hypertension, cardiac disease, and diabetese.[17,18] The quality of life is badly affected in patients of Erectile Dysfunction.[19]

MATERIAL AND METHODS

This was comparative cross-section study completed in six months from April to September 2019. The study was approved by the ethical committee of Khyber Medical University. Patients were enrolled from the Khyber Teaching Hospital Peshawar and Government Naseerullah Babar Memorial Hospital, Peshawar.

The sample size was calculated using the online sample size calculator Raosoft® anticipating 75% prevalence of ED and T2DM patients with confidence level of 95% and margin of error at 0.08. The sample size was calculated to be 100.

Male patients 30 to 65 years of age, with and without Diabetes Mellitus, and patients having type 2 Diabetes mellitus for at least 1 year were included in the study. Those with active comorbidity (e.g., renal failure, liver cirrhosis, malignancy, cardiac failure), and unmarried patients were excluded. Informed consent from patients was obtained.

Architect 2nd Generation Testosterone® (Abbot Diagnostics, Wiesbaden, Germany) kit, (Reference No. 2P13-28) was used for determining serum total testosterone level. To measure serum free testosterone levels, maglumi free testosterone® (Lotus Global, UK, London) kits (Reference No. 130202011) were used. Manufacturer's guidelines were followed for performing the test. Data were entered and analysed on SPSS-23. Frequencies and percentages were calculated for categorical variables. Mean and standard deviation were calculated for continuous variables, i.e., Total and Free Testosterone. Independent sample *t*-test was performed for comparison between two groups.

RESULTS

Mean age of non-diabetic subjects was 39.08±20.02 and it was 54.08±15.02 years. Majority (44.5%) of patients were 40–49 years old. Duration of Erectile Dysfunction was higher in diabetic patients compared to non-diabetics. The total testosterone in serum of diabetics with ED was 493.09±24.9 ng/dl, and 499.53±23.83 in non-diabetic ED patients. The differences were statistically non-significant (p=0.76). Free testosterone was significantly lower in diabetic patients of our study as compared to the non-diabetic ED patients (59.07 pg/ml *vs* 68.25 pg/ml respectively), (p=0.049).

Table-1: Testosterone levels in patients of ED

Parameters	Diabetics	Non-diabetics	p
Total Testosterone (ng/dl)	493.09±24.9	499.53±23.83	0.76
Free Testosterone (pg/ml)	**59.07**±10.98	**68.25**±10.76	0.049

DISCUSSION

Erectile dysfunction is common in men with type 2 diabetes. There is a high prevalence of symptomatic testosterone deficiency in men having type 2 diabetes. Treatment may lead to a significant improvement in quality of life. Erectile dysfunction due to different neurohormonal parameters affects the normal erection physiology. Besides this, different endocrine abnormalities put effect on normal penile erection. In this study we checked the effects of diabetes mellitus on testosterone and its relation to erectile dysfunction.

Androgens are responsible for regulation of sexual health and preservation of libido as well as penile erection upon arousal. The increasing association of ED and progressive decline of testosterone levels with aging does not necessarily imply a causal link. Majority of the early researchers conducted studies to know the effect of deficiency of testosterone level on sexual performance mainly by inhibiting the production or action of male hormones.[1] Testosterone mainly increases sexual desire in men and thus plays important role in erection of penis during sexual intercourse but some studies also show that testosterone directly causes relaxation of penile smooth muscles through release of nitric oxide (NO), RHO-associated protein kinase (ROCK), PDE5 and the adrenergic response.[2,3] The total and free testosterone levels are reportedly not related to the level of sexual desire in men with ED.[4] The free testosterone levels could be related to the quality and frequency of nocturnal erections, and when ED is more severe, it is more probable that free testosterone levels are below the 'normal' limit.[20] Free testosterone is also reduced with increasing age. According to studies, a 75 years old man has approximately 50% less free testosterone level than a 25 years old young man. As the age increases, the SHBG also increases, so that the free testosterone is more likely to bound with SHBG, thus resulting in further decrease of free testosterone in serum.[6]

Another condition which affects testosterone level is diabetes. As per Kapoor *et al*, about 20% of diabetic patients were suffering from hypogonadism and approximately 50% patients had low free testosterone levels than the recommended Guidelines of European Association of Urology.[7] Decreased insulin activity increases peripheral aromatase function in adipose tissue that converts free testosterone to estradiol. This leads to further decrease in serum testosterone level.[8]

Decreased serum testosterone level leads to increase in lipoprotein lipase activity which indirectly enhances the uptake of free fatty acids by adipose tissues promoting the obesity. This ultimately leads to leptin hormone resistance in body causing energy dis-balance and promotes further fats storage in adipocytes. Leptin resistance also reduces the release of luteinizing hormone and testosterone.[9] The plasma levels of free testosterone in our study were significantly lower in diabetic patients. Diabetes reduces steroid hormone production in the long run. This could be a clue to longevity of the condition in diabetics in our study.

Levels of free testosterone were lowered in a recent study in diabetic men with ED as compared to normal population.[21] Interestingly, the severity of ED as

assessed by the International Index of Erectile Function (IIEF) scores correlated with total as well as bioavailable and free testosterone.[21] The important clinical implication is total testosterone in milder forms of ED is not as sensitive as bioavailable or free testosterone measurements.

Testosterone levels were significantly lower in men with type 2 diabetes who failed to respond to sildenafil when compared to responders and that when testosterone therapy was added, the response improved.[22] Testosterone deficiency also produces adverse changes in the architecture of the corpus cavernosum including the arrangement of elastic fibres leading to pathologic alterations contributing to ED.[23] Testosterone restores sildenafil responsiveness in animal models of diabetes-induced ED.[24]

CONCLUSION

The level of free testosterone was significantly reduced in diabetics with ED as compared to healthy subjects with ED. There was no significant difference in total testosterone in diabetic patients with ED as compared to non-diabetic subjects with ED.

LIMITATIONS OF THE STUDY

The sample size was small; a larger sample could have even better findings. A multi-centre study in a broader area, and psychological factors in ED patients could add to the findings. Serum lipid profile must have been included in investigations. The biggest limitation was the social embarrassment felt by the patients with ED as the patients were reluctant to disclose their problem.

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Contribution of Authors:
JH: Concept, Study design, Manuscript writing and review
IS: DNA Extraction
ZA: Data analysis, tabulation
SR: Data collection and analysis, Review
MIS: Data analysis, Results compilation
HS: Bibliography, Statistical analysis