Comparison of Testosterone Levels in Patients With and Without Type 2 Diabetes

Naina Kumari ¹, Anoosha Khan ¹, Usman Shaikh ¹, Kimberly Lobes ², Deepak Kumar ³, FNU Suman ⁴, Naila S. Bhutto ⁵, Faryal Anees ⁶, Simra Shahid ⁷, Amber Rizwan ⁶

¹. Internal Medicine, Dow University of Health Sciences, Karachi, PAK ². Internal Medicine, Liaquat National Hospital and Medical College, Karachi, PAK ³. Internal Medicine, Jinnah Sindh Medical University, Karachi, PAK ⁴. Internal Medicine, Peoples University of Medical Health Sciences for Women, Nawabshah, PAK ⁵. Internal Medicine, Chandka Medical College, Chandka, PAK ⁶. Family Medicine, Jinnah Post Graduate Medical Center, Karachi, PAK

Corresponding author: Amber Rizwan, amber_aljazeera109@hotmail.com

Abstract

Introduction

Hypogonadotropic hypogonadism is a common disorder associated with type 2 diabetes. Hypogonadotropic hypogonadism in type 2 diabetic patients requires further assessment to understand the etiology, and the possible consequences, complications, and treatment. This study aims to highlight the testosterone level in type 2 diabetes mellitus (DM). Moreover, it further emphasizes the association of testosterone with the duration of DM.

Materials and method

This case-control survey was conducted from September 2020 to March 2021 in the outpatient department of internal medicine in a tertiary care hospital in Pakistan. The experiment group included 200 diabetic male participants aged between 30 and 69 years. In the control group, 200 participants without DM were enrolled in the study. The venous blood sample was collected via phlebotomy and sent to the laboratory to test for total testosterone level.

Results

The mean total testosterone level was significantly lower in diabetic patients compared to the non-diabetic patients (8.9 ± 5.1 mmol/L vs. 14.1 ± 7.2 mmol/L; p-value: <0.0001) and the prevalence of androgen deficiency was significantly higher in diabetic patients compared to non-diabetic patients (45.5% vs. 20.5%; p-value: <0.00001). For each age group, the mean total testosterone level was significantly higher in the diabetic group compared to the non-diabetic group. There was a significant decline in mean total testosterone level as the duration of diabetes increased (p-value: 0.01).

Conclusion

Strong interlink between type 2 DM and low testosterone level has once again highlighted the importance of a broader approach toward men presenting in the diabetic clinic and provided a huge ground for prescribing testosterone replacement therapy in hypogonadal men with DM.

Introduction

Hypogonadotropic hypogonadism is a common disorder associated with type 2 diabetes. Hypogonadotropic hypogonadism in type 2 diabetic patients requires further assessment to understand the etiology, and the possible consequences, complications, and treatment [1]. Lower testosterone levels were observed in 25%-50% of men with type 2 diabetes mellitus (DM) [1].

An Australian study including 580 elderly, obese men with type 2 diabetes was conducted, proving that 43% had low total testosterone levels and 53% had low calculated free testosterone levels [2]. Serum testosterone showed an inverse association with age and BMI in these men; however, low testosterone levels were not restricted to these factors along with low circulating testosterone in 20% young and 40% lean men [3]. A meta-analysis of 20 cross-sectional studies, including 850 type 2 diabetic men, proved that total testosterone levels were adequately reduced in diabetics [4]. Subnormal testosterone levels are comparatively uncommon in men with type 1 DM. In another cross-sectional study of 350 Finnish men, sex hormone-binding globulin (SHBG) was proved to have an association with insulin resistance independent of testosterone, which nullified the association of total testosterone with insulin resistance [5]. A Mendelian randomization study proved that SHBG-germline variants were predicted to be a risk factor of type 2 DM [6].
However, men with low testosterone levels have a twofold risk of development of metabolic or type 2 DM [7].

This topic of testosterone and DM is understudied in developing countries. This study aims to highlight the testosterone level in type 2 diabetics. Moreover, it further emphasizes the association of testosterone with the duration of DM.

**Materials And Methods**

This case-control survey was conducted from September 2020 to March 2021 in the outpatient department of internal medicine in a tertiary care hospital in Pakistan. The experiment group included 200 diabetic male participants aged between 30 and 69 years. In the control group, 200 participants without DM were enrolled in the study. Participants were enrolled via consecutive convenient non-probability sampling. Ethical review board approval was taken before enrolling participants in the study. Exclusion criteria included renal disease, chronic liver disease, malignancies, and androgen therapy, as they may negatively impact testosterone levels.

After informed consent, the participant’s age, BMI, and duration of DM was noted in a self-structured questionnaire. The venous blood sample was collected via phlebotomy and sent to the laboratory to test for total testosterone level. The sample was collected in the morning to avoid variation in testosterone levels. Participants with total testosterone less than 8 mmol/L were labeled as androgen deficient [8].

Statistical Package for Social Sciences® software, version 22.0 (SPSS; IBM Corp., Armonk, NY, USA) was used for data analysis. For numerical variables, data were expressed as mean ± standard deviations. Frequencies and percentages were used for categorical variables. Mean testosterone level was compared using an independent t-test. Chi-square was used to compare the prevalence of androgen deficiency between the two groups. ANOVA test was used to compare mean testosterone levels for different groups stratified based on the duration of DM. Data were stratified based on age group and duration of DM. A p-value of less than 0.05 indicated that there is a difference between both groups and the null hypothesis is not valid.

**Results**

Two groups were comparable in terms of their age distribution, smoking history, and BMI (Table 1).

| Characteristics | Diabetic (n=200) | Non-diabetic (n=200) | P-value |
|-----------------|-----------------|---------------------|---------|
| Age group in years |                 |                     |         |
| 30-39           | 17 (8.5%)       | 15 (7.5%)           | 0.9     |
| 40-49           | 35 (17.5%)      | 40 (20.0%)          |         |
| 50-59           | 101 (50.5%)     | 97 (48.5%)          |         |
| 60-69           | 47 (23.4%)      | 48 (24.0%)          |         |
| Smoking         |                 |                     |         |
| Yes             | 92 (46.0%)      | 99 (49.5%)          | 0.48    |
| No              | 108 (54.0%)     | 101 (50.5%)         |         |
| BMI more than 25 kg/m² |             |                     |         |
| Yes             | 57 (28.5%)      | 54 (27.0%)          | 0.11    |
| No              | 143 (71.5%)     | 146 (73.0%)         |         |

**TABLE 1**: Comparison of characteristics of participants

BMI: body mass index, kg/m²: kilogram per square meter

The mean total testosterone level was significantly lower in diabetic patients compared to the non-diabetic patients (8.9 ± 5.1 mmol/L vs. 14.1 ± 7.2 mmol/L; p-value: <0.0001). The prevalence of androgen deficiency was significantly higher in diabetic patients compared to non-diabetic patients (45.5% vs. 20.5%; p-value: <0.00001) (Table 2).
| Values                              | Diabetic (n=200) | Non-diabetic (n=200) | P-value |
|------------------------------------|------------------|----------------------|---------|
| Mean total testosterone level (mmol/L) | 8.9 ± 5.1        | 14.1 ± 7.2           | <0.0001 |
| Androgen deficiency                | 91 (45.5%)       | 41 (20.5%)           | <0.00001|

**TABLE 2: Comparison of mean total testosterone level and androgen deficiency in both groups**

mmol/L: millimoles per liter

For each age group, the mean total testosterone level was significantly higher in the diabetic group compared to the non-diabetic group (Table 3).

| Age group (in years) | Mean total testosterone level (mmol/L) | P-value |
|----------------------|----------------------------------------|---------|
|                      | Diabetic (n=200) | Non-diabetic (n=200) |         |
|                      | 14.2 ± 6.1        | 20.1 ± 7.5           | 0.0018  |
| 30-39                | 11.6 ± 5.7        | 18.2 ± 7.1           | <0.0001 |
| 40-49                | 8.8 ± 5.1         | 14.5 ± 6.2           | <0.0001 |
| 50-59                | 6.8 ± 4.1         | 9.9 ± 5.9            | 0.0038  |
| 60-69                |                        |                      |         |

**TABLE 3: Age-wise comparison of mean serum testosterone levels in both groups**

mmol/L: millimoles per liter

There was a significant decline in mean total testosterone level as the duration of diabetes increased (p-value: 0.01). The mean total testosterone level of participants with a duration of diabetes less than five years was 9.7 ± 5.8 mmol/L. The mean total testosterone level of participants with a duration of diabetes for more than 10 years was 6.8 ± 4.6 mmol/L (Table 4).

| Duration of diabetes | Mean total testosterone level (mmol/L) | P-value |
|----------------------|----------------------------------------|---------|
|                      | Diabetic (n=200) | Non-diabetic (n=200) |         |
| Less than 5 years (n=61) | 9.7 ± 5.8        |                      |         |
| Between 5 and 10 years (n=81) | 8.7 ± 5.4        |                      | 0.01    |
| More than 10 years (n=58) | 6.8 ± 4.6         |                      |         |

**TABLE 4: Correlation of duration of diabetes and mean serum testosterone levels**

mmol/L: millimoles per liter

Discussion

Type 2 DM is an element of danger for impairing sex steroid status and is a risk factor for developing testosterone deficiency. Marked decline in the serum testosterone has been reported in a significant number of men with type 2 DM [9], favoring the results of our study that there is a remarkable decrease in the total serum testosterone level in patients with diabetes than in patients without diabetes i.e. (8.9 ± 5.1 mmol/L vs. 14.1 ± 7.2 mmol/L; p-value: <0.0001). The mean total testosterone was found to be significantly reduced for each age group in diabetics compared to the non-diabetics. Likewise, androgen deficiency was higher in diabetics than non-diabetics. Inverse relation of total serum testosterone level and duration of diabetes have also been noticed. The mean total testosterone level of participants with the duration of diabetes less than five years was 9.7 ± 5.8 mmol/L. The mean total testosterone level of participants with a duration of diabetes for more than 10 years was 6.8 ± 4.6 mmol/L. In contrast to our study, in the Massachusetts Male Aging Study (MMAS) cohort, a 0.4% reduction of total serum testosterone level per year was found in both healthy population and men with chronic diseases, including type 2 DM, but the decline in diabetic subjects
Our study indicates an association between type 2 diabetes and a low level of testosterone. Our study has once again highlighted the importance of a broader approach toward men presenting in the diabetic clinic and provided a huge ground for prescribing testosterone replacement therapy in hypogonadal men with DM. Further studies should be conducted to reproduce more data in support of evidence of improved glucose homeostasis and gonadal function in men with type 2 DM and men with symptoms of androgen deficiency. In these men, the benefit of testosterone supplementation therapy exceeds the correction of symptoms of androgen deficiency and also includes glucose homeostasis and metabolic control.

Conclusions

To the best of our knowledge, this is the first study in a local setting that studied the association between testosterone and diabetes. However, there are few limitations as well. First, the study was conducted in a single center, so the sample size was less diverse. The second limitation was because of the unavailability of a kit to test free testosterone, total serum testosterone was used.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Dow University of Health Science issued approval DUHS/IRB-OFC/2020-41. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors declare that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P: Frequent occurrence of
hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab. 2004, 89:5462-8. 10.1210/jc.2004-0804

2. Grossmann M, Thomas MC, Panagiotopoulos S, et al.: Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab. 2008, 93:1854-40. 10.1210/jc.2007-2177

3. Tint AN, Hoermann R, Wong H, et al.: Association of sex hormone-binding globulin and free testosterone with mortality in men with type 2 diabetes mellitus. Eur J Endocrinol. 2016, 174:59-68. 10.1530/EJE-15-0672

4. Ding EL, Song Y, Malik VS, Liu S: Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA. 2006, 295:1288-99. 10.1001/jama.295.11.1288

5. Rajala UM, Keinänen-Kiukaanniemi SM, Hirso PK, et al.: Associations of total testosterone and sex hormone-binding globulin levels with insulin sensitivity in middle-aged Finnish men. Diabetes Care. 2007, 30:315. 10.2337/dc06-1979

6. Ding EL, Song Y, Manson JE, et al.: Sex hormone-binding globulin and risk of type 2 diabetes in women and men. N Engl J Med. 2009, 361:1152-63. 10.1056/NEJMoa0804381

7. Haffner SM, Shaten J, Stern MP, Smith GD, Kuller L: Low levels of sex hormone-binding globulin and testosterone predict the development of non-insulin-dependent diabetes mellitus in men. MRFIT Research Group. Multiple Risk Factor Intervention Trial. Am J Epidemiol. 1996, 143:889-97. 10.1093/oxfordjournals.aje.a008832

8. Naz S, Mandhan N, Shankar P, Raj K, Memon S: Sensitivity, specificity and accuracy of androgen deficiency in ageing male (ADAM) questionnaire for the clinical detection of androgen deficiency in the male population in Pakistan. Cureus. 2020, 12:e11788. 10.7759/cureus.11788

9. Corona G, Monami M, Rastrelli G, et al.: Type 2 diabetes mellitus and testosterone: a meta-analysis study. Int J Androl. 2011, 34:528-40. 10.1111/j.1365-2605.2010.01115.x

10. Feldman HA, Longcope C, Derby CA, et al.: Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002, 87:589-98. 10.1210/jcem.87.2.8201

11. Soriguer F, Rubio-Martín E, Fernández D, et al.: Testosterone, SHBG and risk of type 2 diabetes in the second evaluation of the Pizarra cohort study. Eur J Clin Invest. 2012, 42:79-85. 10.1111/j.1365-2362.2011.02559.x

12. Al Hayek AA, Khader YS, Jafal S, Khaweja N, Robert AA, Ajlouni K: Prevalence of low testosterone levels in men with type 2 diabetes mellitus: a cross-sectional study. J Family Community Med. 2013, 20:179-86. 10.4103/2230-8229.120006

13. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR: Longitudinal effects of aging on serum total and free testosterone levels in healthy men. J Clin Endocrinol Metab. 2001, 86:724-31. 10.1210/jcem.86.2.7219

14. Grossmann M: Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab. 2011, 96:2341-53. 10.1210/jcem.2011-0118

15. Li C, Ford ES, Li B, Giles WH, Liu S: Association of testosterone and sex hormone-binding globulin with metabolic syndrome and insulin resistance in men. Diabetes Care. 2010, 33:1618-24. 10.2337/dc09-1788

16. Kalyani RR, Gavini S, Dohs AS: Male hypogonadism in systemic disease. Endocrinol Metab Clin North Am. 2007, 36:533-48. 10.1016/j.ecl.2007.05.014

17. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, Kantoff PW: Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002, 87:599-605. 10.1210/jcem.87.2.8299

18. Xu XF, De Pergola G, Björntorp P: Testosterone increases lipolysis and the number of beta-adrenoceptors in male rat adipocytes. Endocrinology. 1991, 128:579-82. 10.1210/endo-128-1-579

19. Ballester J, Muñoz MC, Domínguez J, Rigaú T, Guinovart JJ, Rodriguez-Gil JE: Insulin-dependent diabetes affects testicular function by FSH- and LH-linked mechanisms. J Androl. 2004, 25:706-19. 10.1002/j.1939-4640.2004.tb02845.x

20. Boyanov MA, Boneva Z, Chistov VG: Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male. 2005, 6:1-7.