Original Article

Impact of noninsulin-dependent diabetes mellitus (level of control) on sex hormone profile and erectile function

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a well-established risk factor for erectile dysfunction (ED); the precise impact of glycemic control on male sexual function, including hormonal profiles, remains to be fully elucidated. This study aims to investigate the specific relationship between the degree of glycemic control in T2DM patients and the severity of both hormonal imbalances and ED.

Methodology: A comparative study between two arms – relatively controlled and uncontrolled type 2 diabetic men. We considered a relatively controlled diabetes mellitus (DM), patient with glycated hemoglobin (HbA1c) of 7.9 mmol/L or less. Laboratory results for type 2 diabetic men presenting with ED were studied after stratifying them into the two groups – relatively controlled DM (HBA1c of 7.9 mmol/L or less) and uncontrolled DM (HBA1c equal to or more than 8 mmol/L). Retrieved data include patient's demographics, body mass index (BMI), hormonal profile, Complete Blood Count (CBC), lipid profile, prostate-specific antigen (PSA), urate, Vitamin D level, and the severity of ED as assessed by the International Index of Erectile Function (IIEF) scores. Statistical analysis was done to compare between the two groups using SPSS version 20. $P < 0.05$ was considered statistically significant.

Results: This study found a significant association between poor glycemic control (HbA1c ≥8%) and ED in diabetic men ($P < 0.0001$). Longer diabetes duration correlated with both ED and poor glycemic control, suggesting a potential causal link. Well-controlled diabetics had lower BMI ($P = 0.001$), higher free testosterone (FT) ($P = 0.0002$), lower sex hormone-binding globulin (SHBG) ($P = 0.0001$), and higher IIEF scores ($P < 0.0001$) compared to the poorly controlled group, indicating better erectile function and potential benefits of weight management and improved testosterone availability. While follicle-stimulating hormone and luteinizing hormone levels were not significantly affected, Vitamin D levels were higher in the well-controlled group ($P = 0.0002$), suggesting a potential role for Vitamin D in ED, although further investigation is needed. Cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, PSA, thyroid-stimulating hormone, and T4 levels did not show significant differences but might warrant further exploration.

Conclusion: This study demonstrates an association between poor glycemic control and impaired erectile function in diabetic men. Lower FT levels, elevated SHBG, and increased BMI were observed in the poorly

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controlled group, potentially contributing to ED. Conversely, good glycemic control correlated with improved erectile function, potentially due to higher FT availability and Vitamin D levels.

Keywords: Diabetes mellitus, erectile dysfunction, hemoglobin A1c, hormonal profile

INTRODUCTION

Erectile dysfunction (ED), defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse,[1] is a prevalent concern for men, particularly those exceeding 40 years of age.[2] The incidence of ED is significantly amplified in individuals with diabetes mellitus (DM), demonstrating a 3.5-fold increase compared to those without the condition.[3] The rising prevalence of DM, attributed in part to sedentary lifestyles and escalating obesity rates, further highlights the importance of understanding the underlying mechanisms linking these conditions.[4]

The global burden of DM is substantial, with over 300 million individuals currently afflicted, and projections anticipate this number to surpass 592 million by 2035.[5] This chronic disease is characterized by impaired insulin sensitivity, often accompanied by decreased testosterone levels.[6,7] Numerous studies have established a correlation between type 2 DM (T2DM) and both lower testosterone concentrations and a heightened risk of ED.[8-11] The reported co-occurrence of hypogonadism (low testosterone) and ED in diabetic men ranges from 54% to 94.4%.[12,13]

Despite existing research, a critical gap persists in our understanding of how glycemic control, the management of blood sugar levels in diabetic patients, influences hormonal profiles, and their subsequent impact on erectile function. This investigation aims to address this gap by exploring the potential association between suboptimal glycemic control in diabetic patients and its detrimental effects on hormonal profiles, particularly testosterone levels, and the consequent decline in erectile function.

METHODOLOGY

This study presents a retrospective analysis conducted at our hospital, investigating the association between glycemic control and hormonal profiles in patients with T2DM. The study period spanned from January 2016 to January 2022, focusing on patients with a history of regular follow-up within the andrology and male infertility clinics.

Inclusion criteria aimed to recruit a total of 400 participants, divided equally into two groups based on glycated hemoglobin (HbA1c) levels. Patients underwent two HbA1c measurements separated by a minimum interval of 3 months. Those with the first reading demonstrating an HbA1c of 7.9% or less were categorized as the "relatively controlled diabetic group." Conversely, patients with an HbA1c of 8% or higher in the first reading were classified as the "uncontrolled diabetic group." This classification scheme adhered to the guidelines established by the American Diabetes Association.[14] Any participant with discordant HbA1c readings (i.e. readings not falling within the designated categories) was excluded to ensure group homogeneity.

Demographic data were comprehensively collected for all participants. Following the second HbA1c measurement, a retrospective review was conducted on each patient's clinical data, encompassing body mass index (BMI), smoking status, coexisting medical conditions, and laboratory results encompassing a comprehensive hormonal profile: total testosterone (TT), free testosterone (FT), sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, estradiol, Vitamin D, lipid profile (total cholesterol, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]), thyroid function tests (T4 and thyroid-stimulating hormone [TSH]), and prostate-specific antigen (PSA).

Data analysis was performed using the SPSS version 20 (IBM Corp., Armonk, NY). Continuous variables were characterized by mean and standard deviation, whereas categorical variables were presented as frequencies and percentages. Group comparisons for continuous data were conducted using Student's *t*-test or analysis of variance as appropriate. The Chi-squared tests were employed for comparisons involving categorical variables.

The significance level (*P* value) was set at 0.05. $P < 0.05$ was considered statistically significant, indicating rejection of the null hypothesis (i.e. no difference between the groups). Lower *P* values (e.g. 0.001) reflected stronger evidence against the null hypothesis.

By contrasting patients with HbA1c exceeding 8% (poor control group) to those with HbA1c below 7.9% (controls), the study aimed to elucidate the potential negative

influence of HbA1c levels on both erectile function and the hormonal profile in this patient population.

RESULTS

This study investigated the association between glycemic control and ED in diabetic men. The findings demonstrate a statistically significant correlation between these factors.

Duration of DM is strongly associated with ED ($P < 0.0001$). Men with longer DM duration had a higher prevalence of ED and were more likely to have poor glycemic control (HbA1c ≥8%). This suggests a potential causal link between uncontrolled blood sugar and ED risk.

The well-controlled diabetic group had a significantly lower mean BMI compared to the poorly controlled group ($P = 0.001$), suggesting a potential role of weight management in ED risk.

Patients with good glycemic control had significantly higher mean FT levels and lower mean SHBG levels compared to the poorly controlled group ($P = 0.0002$ and 0.0001, respectively). This indicates better availability of bioactive testosterone in the well-controlled group, potentially influencing erectile function.

Levels of FSH and LH were not significantly influenced by diabetic status, suggesting minimal impact on testicular function.

The well-controlled group exhibited a significantly higher mean International Index of Erectile Function (IIEF) score (indicating better erectile function) compared to the poorly controlled group ($P < 0.0001$). This further strengthens the link between glycemic control and ED.

Patients with good glycemic control had significantly higher Vitamin D levels compared to those with poor control ($P = 0.0002$). This suggests a potential role for Vitamin D in erectile function, although further research is needed to clarify the mechanism.

The study did not observe significant differences in other measured parameters such as cholesterol, LDL, HDL, triglycerides, PSA, TSH, and T4. However, it is important to acknowledge that these factors might play a role in some cases and warrant further investigation [Table 1].

DISCUSSION

Diabetic patients in general have a lot of DM consequences; most of them are well understood as its considered secondary to vasculopathy, but the relationship between DM patients either good or poor controlled and erectile function or sex hormonal profile abnormalities mainly testosterone levels which is not fully investigated in the literature.

Hypogonadism is clearly associated with diabetes, and studies have shown that 20%–50% of men with T2DM have low serum total or FT. The low serum testosterone levels are accompanied by lower serum LH and FSH levels, suggesting that hypogonadotropic hypogonadism is the cause of lower serum testosterone levels in T2DM.[15-18]

However, our study notifies that the levels of FSH/LH are not influenced by diabetic status where both within the normal range which reflects the causes of hypogonadism status are primary rather than secondary.

The literature stated that endogenous TT and FT levels were reduced by up to 43% and 57%, respectively, in males with T2DM.[19]

About 45%–50% of testosterone in adult men's blood are strongly bound to SHBG with high affinity, 50%–55% are weakly bound to albumin, and <2%–3% are unbound. Both unbound and albumin-bound testosterone can act on the target tissues. Androgens inhibit SHBG production while estrogens stimulate it.[20]

We found that patients with well-controlled DM had a higher mean level of FT (37.8 ± 18.8) than patients with poorly controlled DM (31.7 ± 12.9), indicating a negative effect of low FT level on erectile function. The difference was statistically significant with $P = 0.0002$.

We also observed the influence of DM control on SHBG level, which showed an inverse relationship with FT level. The group with well-controlled DM had a lower mean SHBG level of 45.8 ± 23.5, implying a higher FT level, while the group with poorly controlled DM had a higher mean SHBG level of 54.7 ± 22.3, implying a lower FT level. The difference was highly significant with $P = 0.0001$.

Andersson *et al*. reported that's men with noninsulin-dependent diabetes mellitus (NIDDM) had higher fasting plasma insulin concentrations than did the nondiabetic control subjects. Testosterone and SHBG were lower in the diabetic men than in both control groups. The derived value of FT was not different between the groups which not coping our results that the FT is statistically significantly lower in the noncontrolled group.[21]

One meta-analysis shows that the overall Vitamin D deficiency in the healthy Saudi Arabian population is 60%.[22]

We investigate the association between Vitamin D level and erectile function in patients with well-controlled and poorly controlled DM. We found that patients with good glycemic control have higher Vitamin D levels (57.0 ± 30.0), and we thought that patients with a poor controlled diabetic state have a significantly low level of Vitamin D, and we explained this poor diabetic state that may indicate a sedentary lifestyle, low activates, and insufficient sun exposure better erectile function than patients with poor glycemic control (47.2 ± 21.6), with $P = 0.0002$. This suggests a role of Vitamin D in glucose metabolism and testosterone synthesis.

Vitamin D deficiency may affect ED since both conditions are related to vascular dysfunction and cardiovascular impairment.

However, the evidence for this association is weak and inconsistent, as most studies have used small samples and different methods, a recent meta-analysis by Wei *et al*. did not find a strong link between Vitamin D levels and ED risk.[23]

BMI is considered one of the most significant risk factors for DM and many other lethal diseases, and this is the same idea we found in our research where we found that people with uncontrolled diabetic status have higher BMI than relatively controlled groups where BMI of 28.4 ± 5.3 had a lower risk of ED than the group with a higher mean BMI of 30.3 ± 6.1, with a $P = 0.001$.

These results suggest that elevated BMI may adversely impact both erectile function and sex hormone profiles, as supported by a meta-analysis demonstrating a positive correlation between higher BMI and increased diabetic complications in T2DM patients.[24]

Individuals with elevated BMI are at increased risk of developing NIDDM and experiencing alterations in sex hormone profiles, including total testosterone (TT), free testosterone (FT), and sex hormone-binding globulin (SHBG). These hormonal imbalances can adversely impact erectile function. Numerous studies have reported significant negative associations between high BMI and TT, FT, and SHBG levels, corroborating the findings of our investigation.[25]

Upon our review of the literature, there is no study investigating the relation between diabetic control status and its subsequent effect on erectile function.

Our findings observed a significant difference in the prevalence of ED between the two groups of patients, uncontrolled diabetic group IIEF score – 8.2 ± 2.7 while the relatively controlled group IIEF score – 18.4 ± 3, $P < 0.0001$.

Testosterone and SHBG concentrations were lower in men with NIDDM than in control subjects. Lower testosterone and SHBG values have been reported previously in men with an excess of body fat in the abdomen.[26-28]

Our findings confirm that uncontrolled DM is a major risk factor for severe ED and sex hormone profile imbalance, where it affects the erectile function as one of the risks of poor control DM or sex hormone abnormality.

The duration of diabetes is a critical factor influencing glycemic control and erectile function. Prolonged diabetes is associated with poorer glycemic control, as reflected by elevated HbA1c levels, and a higher prevalence of erectile dysfunction. This is supported by numerous studies, including a systematic review (SR) and meta-analysis of 17 studies involving 6002 diabetic participants, which identified the duration of diabetes as a significant risk factor for erectile dysfunction. Duration of DM >10 years, age >40 years, peripheral neuropathy, no physical exercise, testosterone level <8 nmol/l, and peripheral vascular disease were significantly associated with ED among diabetic patients.[29]

Another study done for patients with a long duration of DM (more than 5 years) had a 3.2 times greater odds of developing ED than those patients who had DM for <5 years. A possible explanation for this is that patients living with DM for a longer time have an increased risk of DM-related complications and other comorbidities, as well as poor glycemic control, which can affect sexual function. Moreover, the risk of micro- and macrovascular complications increases over time.[30]

According to Cameron *et al*., chronic exposure to high blood sugar levels causes a significant reduction in serum testosterone which ends with sex hormone profile imbalance and impotence; this is due to the accumulation of lipids in Leydig cells caused by hyperglycemia[31] which agreed to our result which showed that the duration of DM was significantly associated with ED, with $P < 0.0001$, indicating that patients with longer DM duration had a higher risk of developing impotence. We also observed that patients with longer DM duration were more likely to have poor glycemic control.

Inadequate glycemic control in diabetes mellitus is associated with a complex interplay of factors, including low free testosterone (FT), low total testosterone (TT), elevated sex hormone-binding globulin (SHBG) levels, increased Body Mass Index (BMI), and vitamin D deficiency. These factors contribute to the development of severe erectile dysfunction (ED). Effective management of diabetic status may ameliorate these contributing factors and consequently improve erectile function.

We did not observe any significant differences between the groups in terms of the other parameters that we measured, such as cholesterol, LDL, HDL, triglyceride, PSA, TSH, and thyroxine.

CONCLUSION

Men with well-managed diabetes are more likely to have normal testosterone levels and better erectile function. In contrast, poorly controlled diabetes can lead to a drop in testosterone, increased SHBG, and a higher risk of severe ED.

Poor glycemic control can lower FT and TT levels, raise SHBG, increase BMI, and reduce Vitamin D levels. All these factors contribute to significant ED. Fortunately, good diabetes management can improve these factors and potentially restore erectile function.

More research is needed to confirm the effectiveness of diabetes control in improving erectile function for men with uncontrolled diabetes.

Table 1: Comparing between relatively controlled and uncontrolled diabetic group

Parameters	Group 1 (HbA1c <8)	Group 2 (HbA1c ≥8)	*P*
Age	66.8±11.4	65.0±11.1	0.11
Diabetic duration	11.4±4.9	13.9±3.1	<0.0001
HbA1c (%)	6.7±0.7	9.5±1.2	<0.0001
BMI (kg/m^2), mean±SD	28.4±5.3	30.3±6.1	0.001
TT (nmol/L)	16.5±6.5	16.2±12.9	0.77
FT (pmol/L)	37.8±18.8	31.7±12.9	0.0002
SHBG (mmol/L)	45.8±23.5	54.7±22.3	0.0001
Estradiol (pmol/L)	137.1±53.8	133.7±54.2	0.53
FSH (IU/L)	7.6±7.3	7.9±4.5	0.62
LH (IU/L)	8.2±13.2	8.0±6.1	0.85
Prolactin (mIU/L)	201.1±85.3	214.7±119.7	0.19
Vitamin D (nmol/L)	57.0±30.0	47.2±21.6	0.0002
Cholesterol (mmol/L)	4.0±1.1	4.3±2.3	0.097
LDL (mmol/L)	2.4±0.9	2.5±0.8	0.24
HDL (mmol/L)	1.09±0.27	1.05±0.30	0.16
Triglyceride (mmol/L)	1.9±1.5	1.8±0.9	0.42
PSA (micg/L)	1.8±1.9	1.7±1.8	0.59
TSH (IU/L)	3.5±9.7	3.4±5.1	0.896
T4 (pmol/L)	15.4±2.1	15.5±2.6	0.67
IIEF*	18.4±3	8.2±2.7	<0.0001

P-value significant <0.05. Hb: Hemoglobin, HbA1c: Hb A1c, SHBG: Sex hormone binding globulin, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, LDL: Low density lipoprotein, HDL: High density lipoprotein, PSA: Prostate specific antigen, TSH: Thyroid stimulating hormone, T4: Thyroxine, BMI: Body mass index, SD: Standard deviation, TT: Total testosterone, FT: Free testosterone, *IIEF: International index of erectile function

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Conflicts of interest

There are no conflicts of interest.

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