Effect of Low-Dose Tadalafil Once Daily On Glycemic Control In Patients With Type 2 Diabetes and Erectile Dysfunction: A Randomized, Double-blind, Placebo-controlled Pilot Study

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Abstract

Background: Phosphodiesterase type 5 inhibitors restore nitric oxide signaling, which plays a significant role in erectile function and appears to counteract insulin resistance in animal and human models. This study was aimed to evaluate the glycemic and metabolic effects of low-dose tadalafil once a day in patients with type 2 diabetes and erectile dysfunction.

Methods: A 6-month, randomized, double-blind, placebo-controlled pilot trial was conducted. Eligible patients were randomly assigned in a ratio of 2:1 to the tadalafil 5 mg and placebo groups; all patients received either tadalafil or placebo once a day. *The primary efficacy* endpoint was the change in the *glycated hemoglobin* (HbA1c) level during the 6-month study period. The secondary efficacy endpoints included metabolic parameters and erectile function.

Results: Of the 68 patients who completed this study, 45 and 23 patients were allocated in the tadalafil and placebo groups, respectively. The mean HbA1c level was significantly different between the groups over the 6-month study period ($P = 0.021$). After 6 months of treatment, the HbA1c decrement in the tadalafil group was greater than that in the placebo group (-0.14% ± 0.53% vs. 0.20% ± 0.69%, $P = 0.030$). The improvement in the International Index of Erectile Function-5 scores were significantly greater in the tadalafil group than in the placebo group at 6 months ($P = 0.003$).

Conclusion: This prospective pilot study shows that low-dose tadalafil once a day is effective in improving glycemic control and erectile function in patients with type 2 diabetes and erectile dysfunction.

Trial Registration: KCT0005666

Background

Erectile dysfunction (ED) is a common complication of diabetes that is underdiagnosed and mostly left untreated [1]. The prevalence of ED according to the International Index of Erectile Function (IIEF) score is estimated to be >50% in men with diabetes and is approximately 3.5 times higher in men with diabetes than that in those without [2]. Diabetic ED involves vascular and neurological mechanisms [3]. Nitric oxide (NO) plays a significant role in normal penile erection, and a lack of NO in diabetes triggers ED [4]. Phosphodiesterase type 5 (PDE-5) selectively blocks the hydrolysis of cyclic guanosine monophosphate (cGMP) in the penile corpus cavernosum, thus enhancing NO-mediated smooth muscle relaxation, increasing blood flow to the penis, and facilitating erection [5]. PDE-5 inhibitors result in increased levels of cGMP and NO [6]. Exploratory studies have reported the beneficial effects of PDE-5 inhibitors on ED in patients with type 2 diabetes (T2D) [7, 8].

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia that results from defects in insulin secretion, insulin sensitivity, or both [9]. Insulin resistance (IR) is associated with the development of endothelial dysfunction and a reduction in NO bioavailability [10]. In humans, endothelial dysfunction is linked with diabetes mellitus via a mechanism that interrupts the intracellular signaling

pathways of insulin and NO production [11]. Endothelial NO mediates the insulin-induced effects by increasing the intracellular levels of cGMP in human vascular smooth muscle cells [12]. The increase in glucose transport is stimulated by insulin via the endothelium-derived NO/cGMP pathway [13]. Reduced NO synthesis in endothelial cells contributes to impaired insulin action in patients with T2D [14]. Therefore, treatments that amplify NO/cGMP signaling could improve microvascular recruitment and muscle glucose uptake [15]. Moreover, recent evidence from animal models and men with ED suggests that PDE-5 inhibition may have metabolic benefits [16]. Nevertheless, a meta-analysis of PDE-5 inhibitors studies showed little benefit in improving glycemic control [17].

Tadalafil, a drug used to treat ED, selectively inhibits PDE-5 in the penile corpus cavernosum, and it is an important regulator of smooth muscle relaxation by elevating intracellular NO/cGMP levels [18]. Treatment with tadalafil 5 mg once a day (OAD) is highly effective, safe, and well tolerated in patients with ED associated with T2D [19]. A recent meta-analysis confirmed that chronic use of PDE-5 inhibitors is effective in improving endothelial function, measured using brachial artery flow-mediated dilation and endothelial markers in patients with T2D [20]. Further, in a pilot study, tadalafil OAD increased the basal insulin secretion in men with ED [21]. In another previous study, tadalafil improved peripheral microcirculation and glucose uptake in patients with T2D [22]. Overall, these preliminary studies suggest the therapeutic effect of chronic use of tadalafil daily on glycemic control.

We conducted a randomized clinical trial to evaluate the effect of chronic use of low-dose tadalafil OAD on glycemic control and assessed it according to glycated hemoglobin (*HbA1c*) levels and other metabolic effects in patients with T2D patients and ED. Additionally, we assessed the long-term efficacy and safety of tadalafil for the treatment of erectile function.

Methods

Study Design

A randomized, double-blinded, placebo-controlled pilot study was conducted to examine the glycemic and metabolic effects of 6-month treatment with tadalafil 5 mg OAD in patients with T2D and ED. Sample size statistical criteria are not required in a pilot study. All patients were randomized to receive tadalafil or placebo and instructed to use it OAD for 6 months at the same time every day. The allocation list was produced using a dedicated software (ID-net™) via permuted-block randomization with 2:1 allocation and randomly sized blocks. The allocation details were blinded until the full statistical analysis was completed. All patients were monitored during the entire study duration. Treatment compliance was defined as the administration of at least 70% of the required doses between visits.

The present study protocol was reviewed and approved by the Institutional Review Board of of Myongji Hospital (approval No. MJH-16-038). Informed consent was submitted by all subjects when they were enrolled. The study was conducted in accordance with the protocol, the ethical principles stated in the Declaration of Helsinki (revised in 2000) and the applicable laws. This randomized clinical trial registered at the Clinical Research Information Service (CRIS, http://cris.nih.go.kr), number KCT0005666.

Study Participants

Eligible men were recruited from the outpatient clinic of Myongji Hospital, Goyang-si, Gyeonggi-do, Republic of Korea between January 2017 and November 2018. Men aged 35–75 years who had a regular sexual partner and had intercourse ≥1 time in the last month, patients with T2D and ED for >1 year, patients with HbA1c level <9%, and patients with no history of PDE-5 inhibitor use in the last 3 months were included in this study. ED was defined as a history of persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. The exclusion criteria were as follows: use of exogenous insulin, thiazolidinediones, or nitrate; history of malignancy, high-risk cardiovascular disease, and chronic liver or kidney failure; and presence of contraindications to tadalafil. Concomitant medications (such as oral antidiabetic medications, antihypertensives, and statins) were not permitted to be changed between 3 months before study initiation and 1 month after its completion.

Measurements

At baseline, the selection criteria were evaluated and a complete clinical record was obtained from each subject, including data on demographic characteristics, previous medical history, alcohol consumption, smoking status, and other medical conditions. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured in the standing position at the midpoint between the anterior iliac crest and the lower border of the last palpable rib by a single examiner. Blood pressure (BP) was measured twice using a standardized sphygmomanometer with a 5-min rest period.

Venous blood samples were collected in the morning after a >8-h overnight fast. The concentrations of fasting plasma glucose (FPG), insulin, C-peptide, HbA1c, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), *blood urea nitrogen* (BUN), creatinine, aspartate transaminase (AST), and alanine transaminase (ALT) were measured. Homeostatic model assessment (HOMA) is a method of assessing β-cell function and IR from basal FPG and insulin or C-peptide concentrations [23]. The equations are simplified as HOMA-IR = (fasting plasma insulin × FPG)/22.5 [24]. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease study equation. The hexokinase method, an enzymatic method, and a homogenous enzymatic calorimetric test were used for measuring FPG levels, TC and TG levels, and HDL-C and LDL-C levels, respectively. HbA1c levels were measured using the turbidimetric inhibition immunoassay. The values of biochemical variables were measured using a Cobas Modular 6000 analyzer series (Roche Diagnostics, Basel, Switzerland). These variables were checked at baseline and at 6 months. In addition, weight; WC; BP; and FPG, insulin, C-peptide, and HbA1c levels were measured at 3 months.

Questionnaires

The secondary measures of efficacy of the erectile and voiding function included the IIEF-5 score and the International Prostate Symptom Score (IPSS). IIEF-5, the abridged five-item version of the IIEF, is use to

evaluate erectile function [25]. The possible scores of IIEF-5 ranged from 5 to 25. The IPSS is a validated seven-item questionnaire used to assess lower urinary tract symptoms (LUTS). All participants answered self-administered questionnaires at baseline and at 3 and 6 months of treatment.

Safety Assessment

Safety and tolerability were evaluated through adverse event (AE) monitoring throughout the study. The study investigators obtained and recorded all the observed or self-reported AEs and their severity (mild, moderate, or severe). The relationships of AEs with the study medication were established prior to breaking the blind. All patients underwent laboratory tests, vital sign examinations, physical examinations, and 12-lead electrocardiography at baseline and at the end of the trial. Drug adherence was measured using the medication possession ratio, defined as the total number of days covered by filled prescriptions divided by the total number of days of observation.

Statistical Analysis

All the presented analyses were prespecified. The study outcomes of both groups were compared using Student's t-test for continuous variables and Pearson's chi-square test for categorical variables. Data are expressed as the mean ± SD or as numbers (proportion). Repeated measures analysis of variance (ANOVA) was used to monitor differences in HbA1c levels between the groups over the 6-month period. Exploratory data analysis was used to investigate changes in HbA1c levels from baseline at 3 and 6 months in both groups. Pearson's correlation analysis was used to explore the correlations between changes in HbA1c levels and other variables. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS (version 18.0; IBM, Armonk, NY, USA).

Results

Study Execution and Baseline Characteristics of Participants

Eighty-one patients with T2D and ED were randomized to receive tadalafil (n = 50) or placebo (n = 25) for 6 months. Subsequently, five patients from the tadalafil group and two patients from the placebo group were discontinued. In the tadalafil group, three patients were lost to follow-up, and two patients were discontinued. In the placebo group, one patient was lost to follow-up and one patient was discontinued. Overall, 45 subjects in the tadalafil group and 23 subjects in the placebo group completed the trial (Figure 1). The baseline characteristics were well matched between the groups at randomization and study completion (Table 1).

At the baseline, the mean HbA1c level was 6.83% ± 0.77% and 6.77% ± 0.58% in the tadalafil and placebo groups, respectively ($P = 0.747$). There were no significant differences between the groups with regard to age, WC, BMI, BP, FBS level, insulin level, C-peptide level, TC level, LDL-C level, eGFR, AST and ALT levels, diabetes duration, smoking status, and alcohol consumption.

Changes in HbA1c Levels

Repeated measures ANOVA revealed that the mean HbA1c levels were significantly different between the groups over the 6-month study period (P = 0.021; Figure 2). The mean change in the HbA1c level in the tadalafil and placebo groups was -0.138% ± 0.527% and 0.204% ± 0.492%, respectively, at 3 months of treatment (P = 0.012) and -0.137% ± 0.528% and 0.196% ± 0.691%, respectively, at 6-months of treatment (P = 0.030; Table 2).

Changes in Metabolic Parameters

Table 3 shows the changes in metabolic parameters from baseline at 3 and 6 months of treatment in both groups. At 3 and 6 months of treatment, the HOMA-IR score decreased from that at baseline in the tadalafil group, but the change was not significantly different from that in the placebo group. There were no significant differences in WC, BMI, and BP between the groups at 3 and 6 months. The reduction in the FPG level from baseline at 6 months was significantly greater in the tadalafil group than in the placebo group (-6.40 ± 28.53 mg/dL vs. 5.35 ± 17.77 mg/dL, P = 0.046). At 6 months, the change in the ALT level was -1.49 ± 12.01 IU/L in the tadalafil group and 6.17 ± 8.39 IU/L in the placebo group (P = 0.008). There were no significant differences in terms of changes in the TC level, TG level, HDL-C level, LDL-C level, BUN level, creatinine level, and eGFR between the groups at 6 months.

Changes in the International Index of Erectile Function Score and International Prostate Symptom Score

The IIEF-5 score and IPSS at baseline did not differ between the groups (Table 1). However, improvement in the IIEF-5 score was significantly greater in the tadalafil group than in the placebo group at 3 months (5.96 ± 5.26 vs. 0.78 ± 5.82; P = 0.001) and 6 months (6.56 ± 5.32 vs. 2.22 ± 5.73; P = 0.003). There was a numerical reduction in the IPSS in the tadalafil group; however, it was not statistically significant compared to the placebo group.

Adverse Events and Drug Compliance

Tadalafil was well tolerated, and no subject discontinued the study due to treatment-emergent AEs. Overall, there were a higher percentage of patients reporting AEs in the placebo group (n = 2, 8.6%) than in the tadalafil group (n = 2, 4.4%). The reported AEs were myalgia and senile cataract in the tadalafil group and lumbar spinal stenosis and decreased visual acuity in the placebo group. The AEs were mild in severity. The study population had high medication adherence (>80%) during the study period.

Discussion

In this randomized, double-blind, placebo-controlled study, we found that daily administration of 5 mg tadalafil was associated with improved glycemic control in patients with T2D and ED. Repeated measures ANOVA revealed that the mean HbA1c level was significantly different between the tadalafil and placebo groups during the 6-month study period. Additionally, changes in the HbA1c level from the baseline at 3 months and 6 months of treatment were significantly greater in the tadalafil group than in

the placebo group. In addition, the reduction in the FPG level from baseline at 6 months of treatment was greater in the tadalafil group than in the placebo group.

PDE-5 enzymes are present in various tissues; they are present not only in penile erectile tissues but also in blood vessels, platelets, and smooth muscle tissues [26]. Recently accumulated data on chronic use of low-dose PDE-5 inhibitors indicate that low-dose PDE-5 inhibitors can provide additional potential benefits in diverse medical applications in addition to their famed erectogenic action [27, 28]. However, there are limited placebo-controlled data regarding the effects of PDE-5 inhibitors on glycemic control in patients with T2D. The current study demonstrates that long-term use of low-dose tadalafil has a beneficial effect on glycemic control in patients with T2D and ED, assessed using *HbA1c* and FPG levels.

Tadalafil was first approved for low-dose daily administration at 2.5 mg or 5 mg for the treatment of ED, and it has a longer duration of action than other PDE-5 inhibitors [29]. Chronic low-dose tadalafil therapy has favorable effects on systemic endothelial dysfunction [30]. Although we did not show an effect of tadalafil on biomarkers of endothelial dysfunction, tadalafil was found to improve the levels of circulating inflammatory cytokines and chemokines in a diabetic animal model, while improving FPG levels [31]. Moreover, tadalafil improves insulin action on muscle glucose uptake by prolonging NO/cGMP signaling in women with obesity-linked IR [32]. Tadalafil administration could improve beta-cell function in metabolic syndrome, and this was independent of insulin sensitivity [33]. We found an effect of daily low-dose tadalafil treatment on glycemic control. As all patients in this study were men, further studies are required to investigate whether the same effect occurs in women.

In the study, we observed that ALT levels were lower at 6 months in the tadalafil group than in the placebo group. In a previous study, ALT levels were associated with T2D and glucose-lowering drugs decreased ALT levels as tighter blood glucose levels were achieved [34]. In the present study, daily administration of low-dose tadalafil improved erectile function, and there was a statistical difference in the IIEF-5 scores between the tadalafil and placebo groups. Diabetes-associated ED is mostly caused by endothelial dysfunction, but the precise mechanisms are not fully understood. Daily therapy with low-dose tadalafil has been approved for the treatment of LUTS suggestive of clinical benign prostatic hyperplasia by the Food and Drug Administration. However, the efficacy of tadalafil on LUTS was not significant different from that of placebo as reported in other studies [35], which may be due to the small sample size. In the safety assessment, tadalafil was well tolerated, and no subject discontinued the study due to AEs. The reported AEs were mild in severity.

The current study is the largest double blinded trial, longer term follow-up than the previous trials. We found that a small but significant decrease in HbA1c was observed after 6 months. However, our study has limitations. Firstly, since this study included a small sample size, it is limited to generalize the results. We also did not adjust for confounding variables such as lifestyle modification that may affect the result. Secondly, possible mechanisms to support our results is unclear. We measured insulin sensitivity as indexed by HOMA-IR, but there is a lack in information on parameters of insulin secretion capacity,

endothelial markers, and brachial artery flow-mediated dilation. Larger long-term randomized controlled trials are needed to support the hypothesized effects of tadalafil on glycemic control.

Conclusions

This prospective clinical study found that the daily use of tadalafil 5 mg resulted in more favorable HbA1c and FPG levels than the daily use of placebo after 6 months of treatment. Low-dose tadalafil may be used effectively and safely to improve glycemic control and erectile function in patients with T2D and ED. Nevertheless, future randomized controlled studies using larger sample sizes are required to elucidate the underlying mechanisms that might explain the effects of tadalafil on glycemic control.

Abbreviations

ED: Erectile dysfunction; IIEF: International Index of Erectile Function; NO: Nitric oxide; PDE-5: Phosphodiesterase type 5; cGMP: cyclic guanosine monophosphate; T2D: Type 2 diabetes; IR: Insulin resistance; OAD: Once a day; BMI: Body mass index; WC: Waist circumference; BP: Blood pressure; FPG: Fasting plasma glucose; TC: Total cholesterol; HDL: High density lipoprotein; LDL: Low density lipoprotein; TG: triglyceride; BUN: *Blood urea nitrogen*; AST: Aspartate transaminase; ALT: Alanine transaminase; HOMA: Homeostatic model assessment; eGFR: estimated glomerular filtration rate; IPSS: International Prostate Symptom Score; ANOVA: Analysis of variance; AE: Adverse event

Declarations

Availability of data and materials

The data used to support the findings of this research are available on request from the corresponding author.

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Author information

Contributions

M.K.L. and S.C.K. contributed to the study design and data analysis. M.K.L., J.H.L., S.Y.S., S.Y.L., T.Y.J., and S.C.K. collected and organized data. M.K.L. wrote, reviewed, and edited the manuscript. S.C.K.

provided supervision and revised the manuscript. M.K.L., J.H.L., S.Y.S., S.Y.L., T.Y.J., and S.C.K. participated in the analytic discussion of the results. All authors read and approved the final manuscript.

Ethics declarations

Ethics approval and consent to participate

The present study protocol was reviewed and approved by the Institutional Review Board of of Myongji Hospital (approval No. MJH-16-038). The study was conducted in accordance with the protocol, the ethical principles stated in the Declaration of Helsinki (revised in 2000) and the applicable laws.

Consent for publication

The written informed consents for publication were acquired from each participant.

Competing interest

The authors declare no competing interests.

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Tables

Table 1 Baseline characteristics and demographics

	Tadalafil (n = 45)	Placebo (n = 23)	*P* value*
Age (years)	61.80 ± 7.25	58.87 ± 8.99	0.151
IIEF-5	10.47 ± 4.55	9.57 ± 4.11	0.428
IPSS	13.98 ± 5.77	14.47 ± 8.08	0.231
Waist circumference (cm)	86.89 ± 8.96	89.67 ± 6.21	0.187
Body mass index (kg/m^2)	25.51 ± 3.05	26.59 ± 3.69	0.202
Systolic BP (mmHg)	127.84 ± 14.51	129.70 ± 17.57	0.645
Diastolic BP (mmHg)	87.34 ± 11.74	86.68 ± 8.73	0.538
HbA1c (%)	6.83 ± 0.77	6.77 ± 0.58	0.747
Fasting plasma glucose (mg/dL)	128.02 ± 24.95	120.70 ± 18.34	0.203
Insulin (IU/mL)	9.13 ± 9.14	10.04 ± 8.66	0.694
C-peptide (ng/mL)	1.77 ± 0.92	1.70 ± 0.77	0.686
HOMA-IR	3.05 ± 3.32	2.92 ± 2.51	0.870
Total cholesterol (mg/dL)	142.31 ± 28.05	140.43 ± 31.98	0.804
Triglyceride (mg/dL)	140.40 ± 123.55	144.61 ± 54.57	0.877
HDL-C (mg/dL)	44.42 ± 8.13	43.87 ± 9.50	0.803
LDL-C (mg/dL)	76.89 ± 23.32	74.48 ± 26.29	0.701
BUN (mg/dL)	16.10 ± 4.14	15.36 ± 5.84	0.549
Creatinine (mg/dL)	1.0 ± 0.207	1.01 ± 0.29	0.858
eGFR (mL/min/1.73 m^2)	80.88 ± 14.96	83.49 ± 22.39	0.618
AST (IU/L)	27.09 ± 10.38	27.91 ± 13.51	0.781
ALT (IU/L)	28.56 ± 11.52	28.57 ± 10.24	0.997
Diabetes duration (years)	9.47 ± 6.33	8.13 ± 5.57	0.395
Current smoker (%)	14 (31.1)	7 (30.4)	0.954
Current alcohol drinker (%)	27 (62.2)	16 (69.6)	0.549
Number of concomitant anti-hypoglycemic medication, n (%)			
1	3 (6.7)	3 (13.1)	
2	22 (48.9)	11 (47.8)	
≥3	20 (44.4)	9 (39.1)	0.675

Medication treatment for, n (%)			
Hypertension	30 (66.7)	17 (73.9)	0.541
Dyslipidemia	34 (75.6)	17 (73.9)	0.882
Benign prostate hyperplasia	20 (44.4)	9 (39.1)	0.675

Data are presented as mean ± standard deviation or proportion (%).

IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; HOMA-IR, homeostatic model assessment-insulin resistance; eGFR, estimated glomerular filtration rate.

*P values were derived from paired Student's t-test or Pearson's chi-square test.

Table 2 Change from baseline in the HbA1c level (primary end point) at 3 and 6 months in the tadalafil and placebo groups

	3 months from baseline			6 months from baseline		
	Tadalafil (n = 45)	Placebo (n = 23)	P value[a]	Tadalafil (n = 45)	Placebo (n = 23)	P value*
HbA1c, %	-0.138 ± 0.527	0.204 ± 0.492	0.012	-0.137 ± 0.528	0.196 ± 0.691	0.030

Data are presented as mean ± standard deviation.

*P values were derived from Student's t-test.

Table 3 Secondary outcomes during the study follow-up period

	3 months from baseline			6 months from baseline		
	Tadalafil (n = 45)	Placebo (n = 23)	*P* value[a]	Tadalafil (n = 45)	Placebo (n = 23)	*P* value[*]
IIEF-5	5.96 ± 5.26	0.78 ± 5.82	0.001	6.56 ± 5.32	2.22 ± 5.73	0.003
IPSS	-4.34 ± 5.91	-2.77 ± 6.86	0.330	-4.38 ± 5.86	-3.08 ± 7.27	0.428
Waist circumference (cm)	0.544 ± 2.45	0.848 ± 1.73	0.598	0.57 ± 3.61	1.44 ± 2.90	0.322
Body mass index (kg/m^2)	0.10 ± 0.63	1.29 ± 5.81	0.176	0.29 ± 1.62	1.05 ± 5.99	0.429
Systolic BP (mmHg)	2.44 ± 16.67	-2.78 ± 19.33	0.251	-2.04 ± 18.42	-3.65 ± 17.36	0.730
Diastolic BP (mmHg)	1.69 ± 10.88	-0.35 ± 13.73	0.507	-2.44 ± 12.58	1.61 ± 13.87	0.229
Fasting plasma glucose (mg/dL)	-1.40 ± 16.42	4.35 ± 22.09	0.230	-6.40 ± 28.53	5.35 ± 17.77	0.046
Insulin (IU/mL)	-0.88 ± 9.14	0.75 ± 8.90	0.484	-0.78 ± 10.27	0.67 ± 10.92	0.592
C-peptide (ng/mL)	-0.04 ± 0.88	0.21 ± 0.49	0.218	-0.05 ± 0.99	0.18 ± 0.60	0.306
HOMA-IR	-0.46 ± 3.26	0.18 ± 2.62	0.418	-0.51 ± 3.58	0.32 ± 3.32	0.361
Total cholesterol (mg/dL)				-6.47 ± 19.80	1.83 ± 1.67	0.106
Triglyceride (mg/dL)				-12.82 ± 109.27	-7.13 ± 49.25	0.813
HDL-C (mg/dL)				0.24 ± 6.13	1.0 ± 7.65	0.660
LDL-C (mg/dL)				-2.67 ± 14.17	3.87 ± 14.54	0.079
BUN (mg/dL)				1.14 ± 5.15	1.79 ± 4.76	0.616
Creatinine (mg/dL)				-0.047 ± 0.206	-0.065 ± 0.143	0.701
eGFR ($mL/min/1.73\ m^2$)				4.34 ± 9.76	5.85 ± 10.86	0.564
AST (IU/L)				0.27 ± 8.52	2.52 ± 15.49	0.440

ALT (IU/L)	-1.49 ± 12.01	6.17 ± 8.39	0.008

Data are presented as mean ± standard deviation.

IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; HOMA-IR, homeostatic model assessment-insulin resistance; eGFR, estimated glomerular filtration rate.

*P values were derived from Student's t-test.

Figures

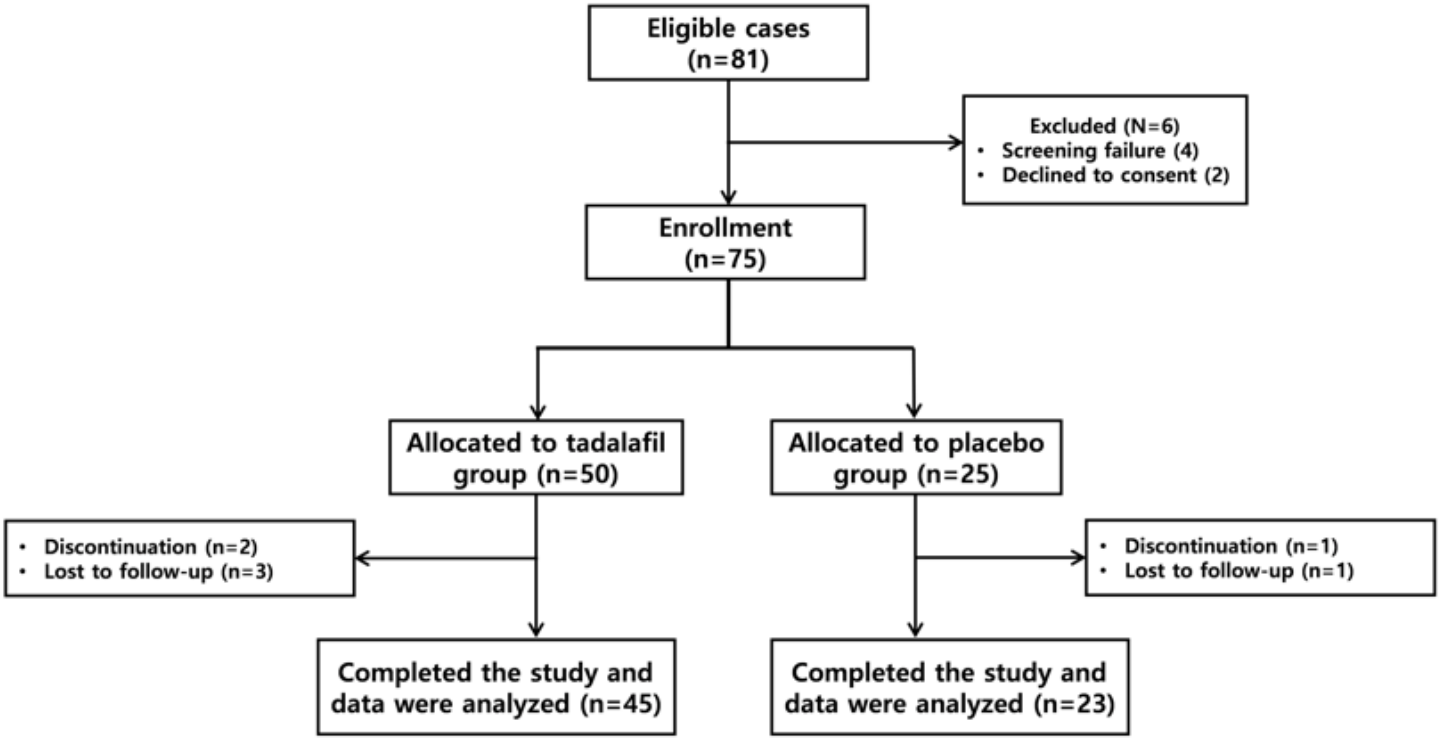

Figure 1

Consort flow diagram The randomization process, treatment, and follow-up of the study participants.

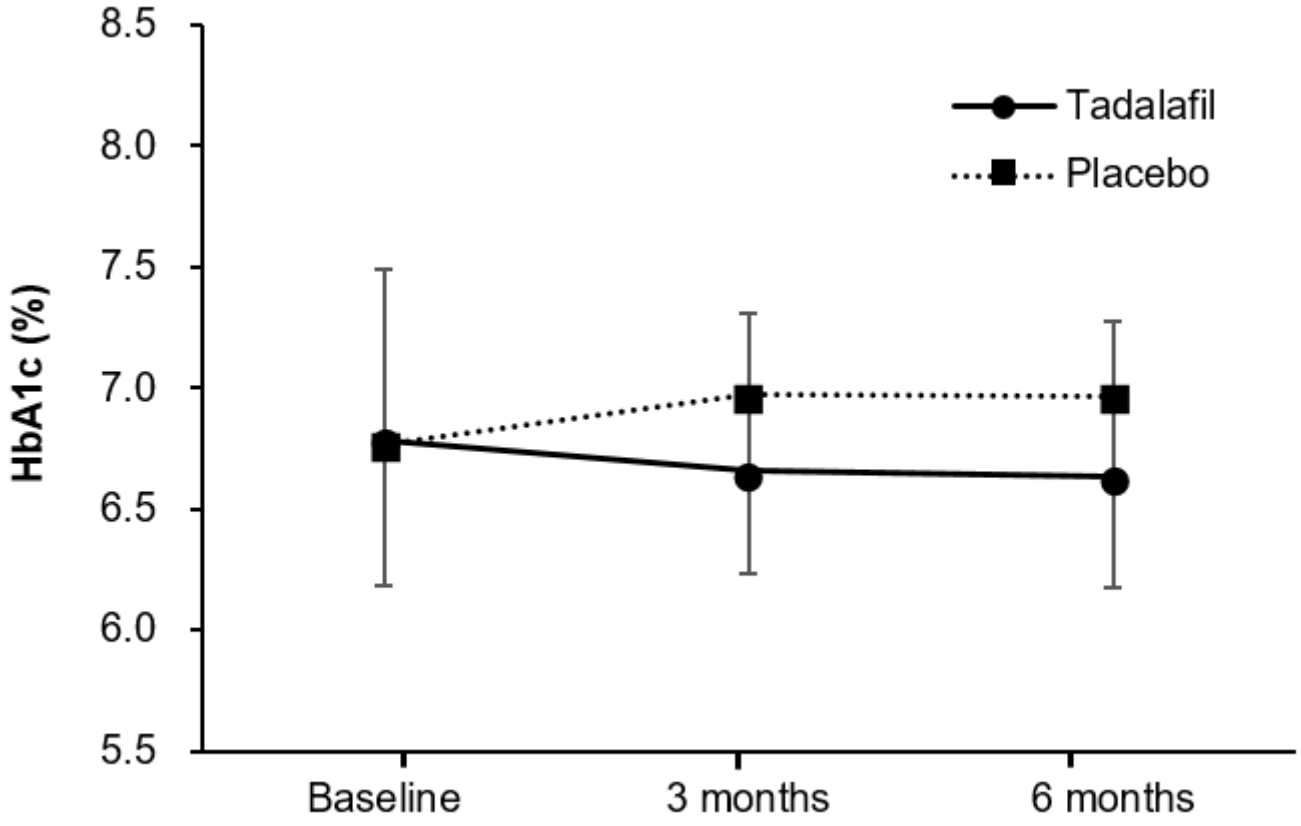

Figure 2

Changes in the HbA1c level over the 6-month study period in the tadalafil and placebo groups Repeated measures analysis of variance revealed significant differences between the groups during the 6-month study period (P = 0.021).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklisttadalafil.pdf