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RESEARCH ARTICLE

Acute effects of sildenafil on flow mediated dilatation and cardiovascular autonomic nerve function in type 2 diabetic patients

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Abstract

Background Sildenafil, frequently used as on demand medication for the treatment of erectile dysfunction (ED), has been suggested to improve endothelial function but also to alter blood pressure (BP) and induce sympathetic activation. In people with type 2 diabetes mellitus (T2DM), a high-risk population, the safety profile and the effects on endothelial function of a maximal sildenafil dose (100 mg) have not been investigated and therefore constituted the aim of our study.

Methods A double-blind, placebo-controlled, cross-over trial using a single dose of 100 mg sildenafil or placebo has been conducted in 40 subjects with T2DM without known CVD. Haemodynamic parameters, flow mediated dilatation (FMD) in brachial artery, cardiovascular autonomic function tests and spontaneous baroreflex sensitivity (BRS) were measured.

Results Sixty minutes after administration of sildenafil but not placebo, a fall of supine systolic blood pressure (SBP) (-5.41 ± 1.87 vs. $+0.54 \pm 1.71$ mmHg) and diastolic blood pressure (DBP) (-4.46 ± 1.13 vs. $+0.89 \pm 0.94$ mmHg), as well as orthostatic SBP (-7.41 ± 2.35 vs. $+0.94 \pm 2.06$ mmHg) and DBP (-5.65 ± 1.45 vs. $+1.76 \pm 1.00$ mmHg) during standing occurred, accompanied by an increase in heart rate ($+1.98 \pm 0.69$ vs. -2.42 ± 0.59 beats/min) (all $p < 0.01$ vs. placebo). Changes in BP to standing up, FMD, time domain and frequency domain indices of heart rate variability (HRV) and BRS were comparable between sildenafil and placebo.

Conclusions Sildenafil administered at a maximum single dose to T2DM men results in a mild increase in heart rate and decrease in BP, but it induces neither an acute improvement of FMD nor any adverse effects on orthostatic BP regulation, HRV and BRS. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords endothelium; sildenafil; baroreceptors; nervous system; autonomic; diabetes

Introduction

Evidence has accumulated indicating that erectile dysfunction (ED) and cardiovascular disease (CVD) share common risk factors such as diabetes mellitus, hypertension, hyperlipidemia, smoking and obesity as well as pathomechanisms like endothelial dysfunction [1]. It was suggested that ED early accompanies endothelial dysfunction [2,3] and that the improvement of ED following treatment is at least partly mediated by an improvement in

endothelial function [1]. Endothelial dysfunction is an early and reversible finding of atherosclerosis [4] and a predictor for cardiovascular risk. Consequently, improvement of endothelial dysfunction was postulated to prevent atherosclerosis [5].

Sildenafil is a selective inhibitor of the cGMP-specific phosphodiesterase type 5 (PDE5) isoenzyme, resulting in prolonged action of cGMP, the primary mediator of vasodilatation in the corpus cavernosum [6]. Although initially developed for the treatment of patients with coronary heart disease (CHD), sildenafil gained major attraction for being the first agent to effectively treat ED [7], a common complication of type 2 diabetes mellitus (T2DM).

Apart from the corpus cavernosum, PDE5 is also expressed in vessel smooth muscle cells, platelets and lung tissue [8]. Therefore, further indications for sildenafil beyond ED treatment have emerged [8]. Recently, sildenafil was approved for the treatment of pulmonary arterial hypertension [8] and several studies suggested improvement in vascular function after acute treatment with Sildenafil in healthy smokers [9], patients with heart failure [10], coronary artery disease [11] or T2DM [6]. The other two available PDE5 inhibitors, tadalafil [12,13] and vardenafil [14], have also been shown to exert beneficial vascular effects. However, it remains controversial whether or not sildenafil improves vascular function, since several studies reported negative results in healthy non-smokers [15] and smokers [16] as well as in patients with coronary heart disease (CHD) [17].

Endothelial function is profoundly impaired in patients with T2DM [18] and, hypothetically, its restoration by sildenafil could be an important step towards prevention of atherosclerosis and cure of ED [6]. However, in the diabetic population the available evidence for a favorable effect of sildenafil on endothelial function is scant [6].

The autonomic nervous system (ANS) plays a paramount role in affecting the cardiac milieu and promoting malignant ventricular activity [19]. Heart rate variability (HRV) and spontaneous baroreflex sensitivity (BRS) are noninvasive tools for assessing the status of the ANS in various diseases. In diabetic patients, reduced HRV is regarded as a hallmark of cardiac autonomic neuropathy (CAN) which represents a serious complication associated with an approximately 2-fold increased mortality, sudden death and silent myocardial ischemia [19].

Serious adverse events related to sildenafil treatment have previously been reported [20], but a clear link could not be demonstrated, since other confounding factors like CHD and concomitant drug therapies have generally also been implicated [21]. A hypothesis for a potentially harmful effect of sidenafil is that a decrease in blood pressure (BP) [22] will trigger a reactive increase in sympathetic activity [23,24]. This might increase heart rates [25] and have a proarrhythmogenic effect by altering QT dynamics [23]. Two studies have shown sildenafil to increase sympathetic-driven heart rate and peripheral BP regulation [23] as well as muscle sympathetic activity and norepinephrine levels [26]. However, another study found no effect of sildenafil on HRV in men with ED and multiple comorbidities [27].

To our knowledge, no data has been published on parasympathetic and sympathetic nerve function following acute sildenafil administration in patients with T2DM, a population with an increased cardiovascular risk per se [28] often taking this treatment. The aim of this study was to evaluate the acute effects of sildenafil on vascular function, hemodynamics and cardiovascular parasympathetic and sympathetic nerve function using time domain and frequency domain indexes of HRV and BRS in type 2 diabetic men without history of CVD.

Research design and methods

Forty consecutive men with T2DM were recruited from the outpatient unit of the German Diabetes Center Duesseldorf. We excluded patients with history of cardiovascular (anamnesis and resting ECG) and malignant disease (anamnesis), advanced nephropathy (creatinine $\geq$2.2 mg/dL), hepatopathy (liver enzymes higher than the double of normal values) and patients taking nitrates. Two patients were lost to follow up (1 accident, 1 withdrawal of consent), three patients were excluded from the analysis of flow mediated dilatation (FMD) alone before unblinding the study due to poor image quality. Patients' demographic and clinical characteristics were (mean $\pm$ SEM): age: 55.1 ± 1.17 years; diabetes duration: 6.4 ± 0.8 years, BMI: 30.8 ± 0.8 kg/m^2; HbA_{1c} : 7.9 ± 0.3%; blood glucose: 144 ± 8 mg/dL, total cholesterol: 169 ± 8 mg/dL, triglycerides: 135 ± 14 mg/dL. ED was present in 32 subjects, and 7 patients were smokers. Diabetic complications included peripheral neuropathy ($n = 12$, diagnosed by neuropathy symptoms score, vibratory and thermal perception threshold measured clinically and computer assisted), cardiac autonomic neuropathy (CAN) ($n = 6$, diagnosed by computer assisted HRV measurements, for details see Methods in Abstract), microalbuminuria ($n = 6$) and retinopathy ($n = 5$). Arterial hypertension (systolic blood pressure (SBP) or diastolic blood pressure (DBP) >135 mmHg or >85 mmHg, respectively) was present in 29 subjects. Twenty-two subjects underwent treatment with ACE-inhibitors or AT-1 receptor blockers ($n = 14$), calcium channel blockers ($n = 2$), beta-blockers ($n = 5$), diuretics ($n = 4$), aspirin ($n = 14$) and statins ($n = 13$). This medication was withdrawn for 24 h before each investigation. Diabetes treatment included diet ($n = 4$), sulfonylureas ($n = 12$), metformin ($n = 23$), glitazones ($n = 3$) and insulin ($n = 11$). Oral medication was withdrawn for 12 h prior to every investigation, long-acting insulin doses were adapted to fasting conditions and administered at similar dose on the two study days (placebo and sildenafil) at least 2 h prior to each investigation.

Before entering the study, informed consent was obtained from all patients according to the 'Declaration of Helsinki'. The study protocol was approved by the ethics

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committee of the Heinrich Heine University, Duesseldorf, Germany.

Patients were investigated using a randomized, double-blind, placebo-controlled cross-over design. The study was unblinded in the presence of a third party after completion of all investigations and when all data were available.

Each patient was investigated three times. During a first visit, FMD was measured and a blood sampling took place. After confirmation of eligibility for the study, two appointments for the main visits were settled, 10 ± 2 days apart. Investigations started at 7 AM, after an overnight fast and withdrawal of medications for at least 12 h (24 h for above mentioned medication), with an FMD measurement, followed by assessment of HRV and BRS. Patients were then asked to take the study medication and to avoid physical activity for 60 min, when investigations were repeated. Alcohol consumption and major physical activity were prohibited for at least 12 h prior to each investigation.

Flow mediated dilatation (FMD)

FMD was assessed at the right brachial artery as previously described [29] using the method established by Celermajer and coworkers [30], by measuring the arterial response to reactive hyperemia causing endothelium-dependent dilatation. In brief, measurements of the right brachial artery diameter were done with a high-resolution, two-dimensional ultrasound imaging system (AUP5, Esaote Biomedica, Genova, Italy) using B-mode, ECG-triggered ultrasound images obtained with a standard 10–13 MHz linear-array transducer. Studies were performed at 21–24 °C in a dark, quiet room with the study subject in a supine position for at least 15 min prior to the first scan and remaining in recumbent position throughout the study. Scanning of the brachial artery was performed 3–10 cm above the antecubital crease, at baseline and 60 s after release of a suprasystolic ischemia of the forearm with a pneumatic tourniquet, inflated at 250 mmHg for 4.5 min. Endothelium-dependent dilatation was defined as the percent change in arterial diameter following reactive hyperemia when compared to the baseline diameter. Images were taken at the end of the diastole and digitalized. All measurements of FMD were performed by two skilled investigators unaware of the status of patients and showed an interobserver variability of $<7\%$.

Heart rate variability (HRV)

Assessment of HRV has been described in detail elsewhere [31] and was performed using the NeuroDiag system (Dr Vetter GmbH, Baden-Baden, Germany). QRS complexes are recognized from the individual electrocardiograms after a learning phase that allows an optimization of detection parameters. The R–R intervals (R–Ri) are measured with an accuracy of ± 1 ms and artefact-free, digitized signal is stored for later analysis. We previously validated a combination of autonomic function tests based on standard, spectral and vector analysis of HRV. This test battery included measurement of the following indexes: coefficient of variation (CV) of R–R intervals, root mean square of successive differences (RMSSD), spectral power in the low-frequency (LF) band (0.04–0.15 Hz) and high-frequency (HF) band (0.15–0.4 Hz), the LF/HF ratio that is generally accepted to reflect the sympathovagal balance [23,32,33]. The age-related normal ranges for these parameters have been previously reported [31].

Orthostatic regulation of blood pressure

BP was assessed with the patient in recumbent position over 1 min using the Dinamap 1846 SX (Critikon, Norderstedt). Then patients were asked to stand up rapidly and measurements were performed six times over further 2 min. The systolic and diastolic difference was calculated as the difference between the last supine value and the lowest value after standing [34].

Blood pressure and pulse interval variability

Following a 10-min rest, BP was continuously measured at the left middle finger using a Finapres 2300-Monitor and a 2300 finger-cuff (Ohmeda, Englewood, CO, USA) with subjects in recumbent position and then after standing up with the hand at the level of the right atrium [35]. The systolic blood pressure (SBP) was digitized at 200 Hz using a Finapres 1.3 Software (ADS Software, Universität Leipzig) and pulse-intervals (PI) were consecutively calculated as surrogates for the R–R intervals. Spectral analysis by fast-Fourier transformation of both SBP and PI was employed to calculate a LF component obtained by integration of values of successive bands from 0.049 to 0.137 Hz and a HF component (associated with respiration) centered on the highest peak detected within the range 0.2–0.5 Hz, with a bandwidth of 0.068 Hz.

Spontaneous baroreflex sensitivity (BRS): cross-spectral analysis

To assess the relationship between SBP and PI variations, a transfer function analysis was applied [35–37]. The coherence and gain for every parameter was calculated. The coherence function quantifies the amount of linear coupling between two time series at any given frequency and has values between 0 and 1. The gain function (ms/mmHg) is the ratio between changes in PI and changes in SBP. The maximum of coherence (Coh) and gain (Gain) were studied in the LF and HF range.

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Sequence method

The sequence method [35,38,39] identifies 'spontaneous' sequences of three or more consecutive beats in which PI progressive increase parallels SBP progressive rise or PI progressive shortening accompanies SBP progressive decreases. The lower detection threshold was set only for BP at 1 mmHg/beat. For each sequence, a linear correlation coefficient between PI and SBP was calculated and the sequence validated when r exceeded 0.85. The percentage of beats (%) involved in such baroreflex sequences and the average slope were calculated for each recording.

Erectile dysfunction (ED)

ED was defined as 'the inability to achieve or maintain an erection sufficient for satisfactory sexual performance' and was assessed by the International Index of Erectile Function-5 [40], which is an abridged five-item version of the IIEF-15 questionnaire, referred to as the Sexual Health Inventory of Men (SHIM). A score $\leq$21 points was considered abnormal.

Laboratory parameters

Blood glucose was measured by the hexokinase-method (Gluco-quant; Roche Diagnostics, Mannheim, Germany) from 20 µL blood taken from the finger tip. HbA1c was determined using high performance liquid chromatography (DIAMAT, BioRad, Muenchen, Germany).

Statistical analysis

Results were expressed as mean ± SEM. Because the parameters of HRV and BRS [23,31] showed log normal distribution, these measures were $\log_{10}$ transformed (exception: heart rate). Pearsons' correlation coefficient was used to test correlations between variables. A two-way repeated-measures analysis of variance (ANOVA) was performed to test parameters' variance as a function of time and treatment (four factors). When the test was significant, a two-tailed paired t-test was used to assess differences at individual time points and to compare the change in parameters during the placebo or drug periods. The level of significance was set uniformly at $\alpha = 0.05$.

Results

Brachial artery diameter was significantly increased after sildenafil administration as compared with placebo ($p < 0.05$). A numerical decrease in FMD was observed following sildenafil intake, while after placebo administration FMD was numerically increased, but the difference between the two periods did not reach statistical significance ($p = 0.064$) (Table 1).

The results of BP, HRV and BRS measurements are shown in Table 2. Overall, sildenafil induced a significant decrease in supine SBP and DBP as compared to placebo ($p < 0.01$). No significant differences between the sildenafil and placebo periods were noted for the changes in SBP and DBP to standing up. In the whole group, there was a mean decrease in BP with standing of −19 mmHg before sildenafil and −20 mmHg before placebo, but not all patients showed a decrease. Overall, there was a reduction in SBP with standing of >20 mmHg in 16 of 40 patients, from them, 9 showed a decrease of >27 mmHg [34]. However, none of our patients had symptoms like dizziness or fainting. A decrease in DBP of >10 mmHg was seen in 14 patients. Overall, 20 subjects presented a decrease in SBP >20 mmHg and/or a decrease in DBP >10 mmHg with standing as a possible sign of asymptomatic orthostatic hypotension. Furthermore, sildenafil administration induced a significant increase in heart rate compared to placebo ($p < 0.01$ vs. placebo for all). Administration of sildenafil did not result in any alterations of the HRV and BRS indexes as compared with placebo intake (Table 2). Blood glucose decreased significantly after placebo administration from 144.0 ± 8.0 to 129.3 ± 6.6 mg/dL ($p < 0.001$) and numerically after sildenafil from 147.8 ± 8.7 to 142.2 ± 8.3 mg/dL ($p = 0.092$ vs. baseline, $p = 0.01$ vs. placebo). Side effects were chest pain in one patient and headache and flush in less than 20% of the patients receiving sildenafil; no side effects were seen after placebo.

Discussion

The main finding of this study is that a single dose administration of 100 mg sildenafil to patients with

Table 1. Brachial artery diameter and FMD

	Before sildenafil		After sildenafil		Before placebo		After placebo	
	Baseline	Reactive	Baseline	Reactive	Baseline	Reactive	Baseline	Reactive
Diameter (mm)	4.22 ± 0.09	4.39 ± 0.10	4.26 ± 0.09	4.41 ± 0.10	4.24 ± 0.09	4.41 ± 0.09	4.21 ± 0.08*	4.39 ± 0.08
Change in diameter (mm)	0.19		0.15		0.17		0.18*	
FMD (%)	4.13 ± 0.28		3.67 ± 029		4.08 ± 0.31		4.42 ± 0.31	
Change in FMD (%)			−0.46				+0.34**	

*$p < 0.05$.
**p = NS vs. Sildenafil

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Table 2. Changes in HR, BP and indexes of HRV and spontaneous BRS following sildenafil or placebo

HRV	Before sildenafil	After sildenafil	Before placebo	After placebo
Heart rate (beats/min)	68.98 ± 1.74	70.95 ± 1.84*, **	68.66 ± 1.73	66.24 ± 1.58*
LF power (ms^2)	2.54 ± 0.07	2.65 ± 0.07	2.61 ± 0.09	2.67 ± 0.08
HF power (ms^2)	1.84 ± 0.11	1.91 ± 0.11	1.93 ± 0.11	1.98 ± 0.10
LF/HF ratio	1.50 ± 0.07	1.51 ± 0.07	1.42 ± 0.06	1.41 ± 0.05
RMSSD	1.20 ± 0.05	1.19 ± 0.06	1.25 ± 0.06	1.31 ± 0.05
BRS				
Supine SBP LF power ($mmHg^2$)	0.94 ± 0.05	0.98 ± 0.06	0, 92 ± 0.07	1.00 ± 0.07
Standing SBP LF power ($mmHg^2$)	1.18 ± 0.06	1.24 ± 0.05	1.24 ± 0.06	1.22 ± 0.05
Supine SBP HF power ($mmHg^2$)	0.35 ± 0.06	0.36 ± 0.06	0.39 ± 0.06	0.38 ± 0.07
Standing SBP HF power ($mmHg^2$)	0.56 ± 0.05	0.52 ± 0.07	0.59 ± 0.06	0.53 ± 0.05
Supine HRV LF power (ms^2)	2.45 ± 0.07	2.44 ± 2.23	2.36 ± 0.09	2.47 ± 0.09
Standing HRV LF power (ms^2)	2.29 ± 0.09	2.23 ± 0.08	2.31 ± 0.09	2.24 ± 0.08
Supine HRV HF power (ms^2)	2.14 ± 0.08	2.07 ± 0.09	2.02 ± 0.09	2.16 ± 0.09*
Standing HRV HF power (ms^2)	1.69 ± 0.06	1.56 ± 0.07	1.69 ± 0.07	1.65 ± 0.06
Supine LF gain (ms/mmHg)	0.64 ± 0.03	0.62 ± 0.03	0.58 ± 0.04	0.61 ± 0.04
Standing LF gain (ms/mmHg)	0.39 ± 0.04	0.36 ± 0.04	0.41 ± 0.05	0.39 ± 0.04
Supine HF gain (ms/mmHg)	0.69 ± 0.04	0.64 ± 0.05	0.62 ± 0.05	0.73 ± 0.04*
Standing HF gain (ms/mmHg)	0.33 ± 0.04	0.28 ± 0.05	0.31 ± 0.04	0.33 ± 0.04
Supine slope (ms/mmHg)	0.88 ± 0.03	0.87 ± 0.03	0.83 ± 0.03	0.91 ± 0.03
Standing slope (ms/mmHg)	0.67 ± 0.03	0.64 ± 0.03	0.63 ± 0.03	0.64 ± 0.03
Blood pressure (BP)				
Supine SBP (mmHg)	147.97 ± 2.89	142.58 ± 2.84*, **	149.76 ± 2.84	150.30 ± 2.77
Supine DBP (mmHg)	85.84 ± 1.17	81.38 ± 1.29*, **	85.65 ± 1.25	86.54 ± 1.10
Standing SBP (mmHg)	128.73 ± 3.53	121.32 ± 3.35*, **	129.76 ± 3.39	130.70 ± 3.02
Standing DBP (mmHg)	77.46 ± 1.53	71.81 ± 1.73*, **	77.08 ± 1.51	78.84 ± 1.32
Orthostatic SBP (mmHg)[a]	−19.24 ± 2.33	−21.24 ± 2.27	−20.00 ± 1.95	−19.59 ± 1.45
Orthostatic DBP (mmHg)[a]	−8.38 ± 1.41	−9.57 ± 1.36	−8.57 ± 0.96	−7.70 ± 0.89

All values of HRV (excepting heart rate) and BRS have been $\log_{10}$ transformed
*$p < 0.05$ vs. baseline.
**$p < 0.05$ vs. placebo.
[a]Change in systolic and diastolic blood pressure (SBP, DBP) to standing up.

T2DM, despite producing a mild decrease in BP and increase in heart rate, neither triggers a sympathetic activation nor exacerbates orthostatic hypotension as assessed by extensive characterization of parasympathetic and sympathetic nerve activity using time domain and frequency domain indexes. The lack of effect of sildenafil on FMD in men with T2DM does not confirm an earlier finding [6], but adds to the controversy as to whether PDE5 inhibitors may improve endothelial dysfunction in diabetes and other conditions.

Even though recent data suggest superiority of chronic treatment with PDE5 inhibitors vs. on-demand therapy [12,13], the latter prevails. This is one reason why we have chosen a single application of sildenafil instead of a chronic one. The second reason is that side effects are more probable to occur when the organism is not used to the medication. The purpose of our study was to investigate the safety profile of the maximal dose of sildenafil (100 mg). However, this dose is not suitable for chronic treatment and was the third reason for our choice.

In the present study, administration of 100 mg sildenafil produced a statistically significant albeit relatively small decrease in supine and orthostatic SBP and DBP, without altering the orthostatic BP regulation accompanied by an increase in heart rate (HR). Although previous studies also showed a decrease in SBP and DBP [25,41–43], increase in HR [44] or preservation of orthostatic BP regulation, they were performed either in non-diabetic patients [25,41] or on mixed populations [27,42–44], had a study design other than being placebo-controlled and double-blind [13,25,41,44], or used a lower sildenafil dose [25,42,44]. To our knowledge our study is the first that investigated in a randomized, double-blind, cross-over design the safety profile of the maximum dose of sildenafil in a group of T2DM men.

Sildenafil was reported to induce sympathetic activation in patients with chronic heart failure [23] and in healthy subjects [26], supporting a hypothesis that treatment with PDE5 inhibitors might facilitate cardiovascular events. Even though the safety profile of sildenafil has been extensively reviewed in patients with ED [45] and ischemic heart disease [46] and no clear relation to cardiovascular events was found, the need for careful evaluation of the indication for treatment in high-risk populations was emphasised. Although free of major CVD, the patients studied herein must be considered a high-risk population [28]. In light of the considerable number of men with T2DM using sildenafil, establishing the safety profile in this patients group is an important task. Our study contributes to this context by demonstrating for the first time in men with T2DM that, even at its maximum dose, sildenafil does not induce sympathetic activation. Our data are also in agreement with the study by Angelik *et al.* [27] who reported no effects of sildenafil on measures of the autonomic nervous system (ANS) in men with ED and various comorbidities. However, in that study only 4 of 21 subjects had diabetes, the maximal dose was 50 mg, and there was no placebo arm.

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In the present study, 100 mg sildenafil did not acutely improve FMD in a group of hypertensive T2DM patients. Our data are in contradiction with those published by Desouza *et al*. [6] who showed a marked increase in FMD following sildenafil administration. A direct comparison with that study is difficult due to following aspects: the dose used was 100 mg in our study and 25 mg in theirs, on average our population was older (54 vs. 44 years) and had a higher SBP (150 vs. 128 mmHg) and a markedly lower mean FMD (4.5% vs. 8%). FMD was surprisingly high in the study of Desouza *et al*. [6], a study that included T2DM patients with ED, two conditions known to impair both endothelial function [2,18]. Further studies showing positive effects of PDE5 on endothelial function have not investigated specifically people with diabetes [9–14,47–49] and were not placebo-controlled [9,13,14].

A possible explanation for the lack of improvement in FMD in response to sildenafil may be that 1 h after administration an increase in the baseline brachial artery diameter was observed. This vasodilating effect may have been responsible for a lesser susceptibility of the arterial wall to dilate in response to the postischaemic flow increase. It is known that a higher baseline diameter is associated with a lower postocclusive diameter increment [50]. Indeed, when compared to the pre-treatment state, a numerical but non-significant trend to postocclusive diameter increase following sildenafil was seen (from 4.39 ± 0.1 to 4.41 ± 0.1 mm). Furthermore, the possibility cannot be ruled out that the significant decrease in blood glucose following the administration of placebo as opposed to sildenafil may have contributed to the numerical improvement in FMD in the placebo group. It is known that hyperglycemia induces endothelial dysfunction and attempts to reduce it result in preservation of endothelial function [51]. While the decrease in blood glucose following placebo (−15 mg/dL) can be explained by the physiologic variation in subjects with type 2 diabetes (who have decreased insulin sensitivity in the morning, a finding that improves towards noon), it remains unknown why this effect was less pronounced (−5 mg/dL) following sildenafil administration. However, we do not believe that the difference in blood glucose excursions between placebo and verum influenced the outcomes of our study because (1) there was no correlation between changes in blood glucose and any measured parameter, (2) except FMD, all other parameters behaved similar after sildenafil and placebo despite the difference in blood glucose and (3) the difference itself (10 mg/dL) is small considering the habitual excursions in subjects with diabetes.

On the other hand, our finding is not entirely surprising, since the response rates to PDE5 inhibitors in men with diabetes are known to be lower than in men with other ED aetiologies, possibly because of their profoundly altered endothelial function [52]. It is also conceivable that a single administration is not sufficient to improve vascular function and, hence, longer-term treatment with PDE5 inhibitors is required as recently suggested [12,13,47,53]. Our data are in agreement with studies showing no effect of a single dose of sildenafil on endothelial function in smokers [16], healthy subjects [15], people with diabetes [54] and coronary heart disease (CHD) [17].

Our study has several limitations. We did not measure a systemic index of sympathetic activity, such as plasma norepinephrine or dihydroxyphenylglycol (DHPG). Parameters based on spectral anylyses of HRV or BRS have been shown to mirror sympathetic and parasympathetic function and interplay [19,32]. As a parameter of sympathovagal balance, especially the LF/HF ratio has received consideration [32,33]. However, they are not entirely characterizing the adrenergic component of baroreflex or systemic adrenergic status [55]. Therefore, our study might not completely cover the spectrum of adrenergic changes induced by Sildenafil administration. Consistent with this, patients with impaired adrenergic BRS might be much more susceptible to an orthostatic fall in BP following Sildenafil. This aspect should be addressed in further research. On the other hand, systemic measurements of neuromediators like norepinephrine have been also suggested to have their limitations in mirroring acute changes of autonomic nervous function [56]. Especially, the sensitivity seems to vary with age and integrity of the autonomic system [56]. Therefore, we consider that our study has a reasonable sensitivity for assessing autonomic nervous changes in the population studied. However, the limitations should be kept in mind.

In conclusion, in patients with T2DM without CVD, administration of a single maximum dose of sildenafil, which is usually used by diabetic men with ED as on-demand treatment, does not induce any adverse effects on cardiovascular autonomic nerve function including orthostatic BP regulation but does not appear to improve endothelial function as assessed by FMD.

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Conflict of interest

The authors do not have financial interests related to the study medication to disclose.

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