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ORIGINAL ARTICLE

Relationship between chronic tadalafil administration and improvement of endothelial function in men with erectile dysfunction: a pilot study

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Men with erectile dysfunction (ED) frequently have a disproportionate burden of comorbid vascular disorders including atherosclerotic disease. We investigated whether scheduled tadalafil is better than on-demand (OD) in improving endothelium-dependent vasodilatation of cavernous arteries in men with ED and whether this effect is also exerted on markers of endothelial function. We did an open-label, randomized, crossover study including 20 male outclinic patients aged 18 years or older (mean age 54 years) who had at least a 3-month history of ED of any severity or etiology. Tadalafil (20 mg) on alternate days (ADs) or OD was administered for 4 weeks. Primary end points were variations of basal inflow (peak systolic velocity (PSV)) and flow-mediated dilatation (FMD) of cavernous arteries compared with baseline at penile Duplex ultrasound. Secondary end points were variations of Q13-SIEDY scores regarding morning erections and of markers of endothelial function, that is, vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecule, endothelin-1 (ET-1), insulin and C-reactive protein (CRP). PSVs and FMD were higher after AD treatment when compared with OD and baseline, respectively ($P=0.0001$), and improvements were maintained from 2 weeks after discontinuation ($P<0.005$). Patients receiving tadalafil AD experienced a significant improvement of morning erections as compared to AD treatment ($P<0.0001$); ET1, VCAM and CRP showed a robust decrease after chronic vs OD regimes ($P<0.05$), with concomitant increase in insulin levels ($P<0.05$), without any variation in blood pressure and other laboratory parameters. Chronic but not OD tadalafil improves endothelial function with sustained effects from its discontinuation. Chronic treatment also produces a dramatic increase in morning erections, which determines better oxygenation to the penis, thus providing a rationale for vascular rehabilitation.
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Introduction

A large body of evidence has accumulated to suggest that the impairment of vascular endothelial function is an initial step towards the development of atherosclerosis and that endothelial function is impaired in patients with overt atherosclerotic disease as well as in those at increased cardiovascular risk.[1–4] Flow-mediated dilatation (FMD) induced by reactive hyperemia has been shown to be endothelium-dependent and can be assessed by high-resolution ultrasound in superficial arteries for the non-invasive assessment of endothelial function *in vivo*.[5]

Erectile dysfunction (ED) is common in men with vascular disease and cardiovascular risk factors,[6,7] and in these patients endothelial dysfunction is an important abnormality that contributes to a decrease in penile vascular responses to sexual stimuli. The concept that long-term antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors has been proven to induce both a regression of vascular structure and a reduction in mean arterial pressure, has been recently questioned.[8] Further, the vascular changes that persist off-treatment have been proposed to result from extended inhibition of the trophic actions of angiotensin II, prolonged reduction in mean arterial pressure or from combined

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effects. Recent evidences suggest that aggressive short-term antihypertensive as well as lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may induce structural remodeling of the penile vasculature.[9]

With effectiveness that lasts up to 36 h, tadalafil could provide nearly continuous coverage when taken on a regular basis, allowing patients to choose when to have sexual intercourse. We have recently demonstrated that scheduled tadalafil administration has favorable effects on vessel wall and remodeling that persists even 15 days after withdrawal of treatment in men with increased cardiovascular risk factors regardless of ED.[10] The present study was designed to assess whether scheduled therapy with tadalafil is better than on-demand (OD) in improving endothelial and arterial function in patients with ED of any origin and whether this effect is exerted also on markers of endothelial function.

Methods

Study design

This open-label, randomized, crossover study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 2002, and applicable laws. This study compared the efficacy of a fixed dose of tadalafil (20 mg) (Cialis, Lilly Icos, Indianapolis, IN, USA) taken OD or on alternate days (ADs) for 4 weeks on cavernous endothelium in men with ED previously responding to any phosphodiesterase type-5 inhibitor. Medical history, physical examination, laboratory safety tests and an electrocardiogram were performed at the screening visit. Patients who met all enrollment criteria were randomly allocated to one of the two treatment sequences. Efficacy was measured by monitoring biomarkers of endothelial function at the end of each treatment period and after 15 days withdrawal. Adverse events were collected throughout the treatment phase, including the 1–2-weeks washout period, and during the extension phase (post-treatment). The first phase of the study was a 4-week run-in, treatment-free period (Figure 1). The treatment phase consisted of two treatment periods in which the patient followed either an OD treatment regimen or every other day regimen for a period of 4 weeks, washout for 2 weeks, and then followed the opposite treatment regimen for a period of 4 weeks. Patients followed protocol instructions which included no restrictions on food or alcohol intake. OD dosing was the discretionary administration of tadalafil (20 mg) before potential sexual activity at a maximum frequency of eight doses per month. The ADs dosing was the administration of tadalafil (20 mg) on Monday, Wednesday, Friday and Sunday followed by Tuesday, Thursday and Saturday at a similar time each day, independent of sexual activity. Based on tadalafil's half-life (17.5 hs), we postulated that using alternate dosing of tadalafil, steady-state serum concentrations were attained within 5 days and exposure at steady state was approximately 1.6-fold greater that after a single dose (Lilly-ICOS, data on file). Patients were randomized to receive both regimens, OD and ADs, in a crossover fashion.

Patient population

Study participants were male patients at least 18 years of age and had at least a 3 months history of ED of any severity (mild, moderate or severe) or etiology (psychogenic, organic or mixed) (Table 1). At screening visit, patients were interviewed by the SIEDY, a structured interview originally designed for the pathogenetic assessment of patients complaining ED and provides scores on organic, relational and intrapsychic domains.[11] Question 13 (Q13) of the interview regarding morning erections ('In the last four weeks, did it ever occur to you to wake up with an erection?') along with relative scoring (0 = yes, regularly; 1 = less frequently than before; 2 = occasionally; 3 = never) was designated as secondary end point to evaluate improvements

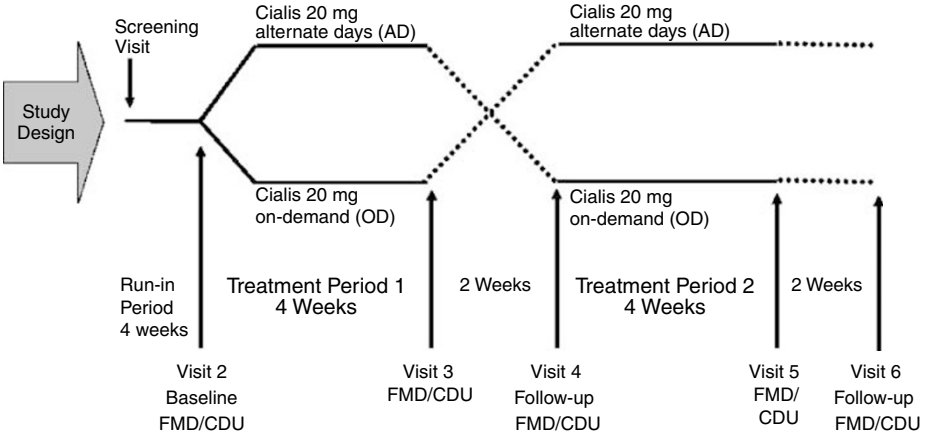

Figure 1 Design of the study.

Table 1 Clinical features of study population at baseline

Patients	$N=20$					
Mean age (years)	54 ± 8					
BMI (kg/m^2)	25.4 ± 3.6					
SIEDY score		*Organic*	*Relational*	*Psychogenic*		
		3.93 (0–9)	2.53 (0–8)	3.33 (0–5)		
Risk factors for ED		*Tryglicerides*	*LDL-Chol*	*HDL-Chol*	*HbA1c*	*Glucose*
Hypercholesterolemia	6 (S)	1.64 [1.4–1.9]	3.13 ± 0.21	1.31 ± 0.20	—	5.59 [5.3–6.0]
Diabetes type II	4 (OH)	1.51 [1.3–2.0]	3.06 ± 0.45	1.33 ± 0.24	6.85 ± 0.47	7.92 [7.0–8.0]
Hypertension (>135/85 mm Hg)	4 (AH)	1.21 [1.1–1.6]	2.99 ± 0.31	1.79 ± 0.38	—	5.38 [5.2–5.9]
Cigarette smoking	4	1.37 [1.2–1.5]	3.04 ± 0.25	1.41 ± 0.13	—	5.24 [5.3–5.7]
Psychogenic	2	1.38 [1.1–1.5]	3.11 ± 0.20	1.50 ± 0.21	—	5.25 [5.2–5.5]

Abbreviations: AH, anti-hypertensives; BMI, body mass index; ED, erectile dysfunction; HDL-Chol, high-density lipoprotein-cholesterol; LDL-Chol, low-density lipoprotein-cholesterol; OH, oral hypoglycemic drugs; S, statins; SIEDY, Semi-structured Interview on Erectile Dysfunction.
Overall, 14 patients were under active concurrent drug treatment. Data are expressed as mean$\pm$s.d. when normally distributed, median [quartiles] when non-normally distributed.
Normal values: tryglicerides <1.80 mmol/l; LDL-Chol <3.36 mmol/l; HDL-Chol >1.55 mmol/l; HbA1c <6%; Glucose <6.99 mmol/l; the range in parentheses indicates the number of subjects under active drug treatments.

obtained by the patients during each treatment period. Patients then agreed not to use any other ED treatment during the run-in period (before receiving the initial dose of study medication), during the treatment phase of the study, and for 48 h after the final study visit. Key exclusion criteria for this study were patients receiving treatment with nitrates, cancer chemotherapy or anti-androgens, or with symptomatic congestive heart failure, hyperhomocysteinemia or other conditions, or drugs impairing endothelium-dependent vasorelaxation, that is, concomitant use of omega-3, carnitine, arginine. Patients who previously used another commercially available phosphodiesterase type-5 inhibitor (PDE5i) were not excluded from this study as well as those who were under treatment of concurrent active drugs (statins, antihypertensives, hypoglycemic drugs; see Table 1) and a good control of their underlying disease was mandatory for enrollment in the study.

Measures

Evaluation of cavernous arteries reactivity. Patients were studied six times: at baseline, at the end of each treatment period and 2 weeks after the last treatment dose. At each study visit, patients underwent study of FMD of cavernous arteries according to the modified procedure of Virag *et al*.[5] and samplings for the evaluation of C-reactive protein (CRP), endothelin-1 (ET-1), insulin, vascular cell adhesion molecule (VCAM) and intercellular cell adhesion molecule (ICAM) levels. All studies were conducted in quiet and temperature-controlled rooms (22–23°C) and peak systolic velocities (PSVs) were recorded at the crura in duplicate according to a previously published procedure.[12] FMD (endothelium-dependent) vasodilatation of cavernous artery were measured by an experienced investigator, unaware of the clinical data. The same investigator performed the three studies in each patient in order to avoid inter-observer variability. Patients were asked to avoid caffeine-containing drinks and to refrain from smoking for the 6 h as well as from tadalafil assumption for the 48 h preceding the study. Imaging studies of the left cavernous artery were performed using a PHILIPS HDI 5000 ultrasound machine equipped with a 7.5–13 MHz broadband linear array transducer. In brief, patients were studied in the supine position and after 15 min rest, the right cavernous artery was scanned over a longitudinal section 1 cm above the crura. A pneumatic tourniquet was placed around the base of the penis and was inflated to a pressure of 220 mm Hg for 5 min. Reactive hyperemia was induced by sudden cuff deflation. The changes in diameter of the left cavernous artery were measured at rest and during reactive hyperemia. A scan was performed continuously for 30 s before and for 150 s after cuff deflation. Fifteen minutes later, a third scan was recorded to confirm vessel recovery. All measurements were performed offline by an experienced operator unaware of the clinical data (AA). The diameter change was expressed as the percent change compared to baseline. Flow velocity profile was also recorded at 15 s intervals. Mean flow velocity was calculated by measurement of the area under the velocity profile curve. Blood flow (ml/min) was calculated from vessel cross-sectional area and cavernous artery blood flow velocity. The intima–media thickness (IMT) was measured by a trained vascular technologist (AA) with the patient supine and the head rotated approximately 45° away from the side being scanned. A segment was scanned bilaterally of the common carotid artery 1 cm distal to the carotid bifurcation during diastole. The best image was selected and two measurements were taken for the same segment of the common carotid artery with a length of 0.5 cm. This process was repeated for the adjacent segment of 0.5 cm and

the mean IMT of the two segments was calculated. According to literature, a value of IMT <0.9 mm was considered normal, whereas a 0.9–1.2 mm range of IMT was defined as increased thickness and IMT >1.3 mm was defined as plaque.[13]

Laboratory analysis. At each visit (Figure 1), 10 ml of blood was withdrawn in the morning after an overnight fasting and assayed for blood glucose (by glucose oxidase method, Aeroset Abbott, Rome, Italy), total and high-density lipoprotein cholesterol, triglyceride (by automated enzymatic colorimetric method; Aeroset Abbott, Rome, Italy) and glycated hemoglobin (HbA1c; high-pressure liquid chromatography method, with upper limit of the normal range of 5.9%; Menarini Diagnostics, Florence, Italy). Blood was then collected in 5 ml tubes with 2% ethylenediaminetetraacetic acid and 500 IU aprotinin. Plasma samples obtained were thawed and assayed for CRP by use of a high-sensitivity assay with a coefficient of variation below 5% (Dade Behring). ET-1 was extracted through absorption column cartridge (Sep-pack C18, Waters, Milford, MA, USA) and measured by radioimmunoassay; intra- and interassay coefficients of variation were 3 and 6%, respectively. Serum insulin was measured using specific immunoradiometric assay (Medgenix Diagnostics, Fleunes, Belgium) in which proinsulin did not crossreact. The intra- and interassay coefficients of variation were 6 and 7%, respectively. Endothelial cell activation was determined by quantization of ICAM and VCAM levels throughout the different treatments, by using enzyme-linked immunosorbent assay measurements; intra- and interassay coefficients of variation were 3.3 and 6%, and 4.3 and 8.5%, respectively.

Statistical analysis. Data are presented as mean $\pm$ s.d. when normally distributed, and as median (quartiles) for nonparametric or percentages when appropriate, unless otherwise specified. After testing data for normality, Student's t test and Wilcoxon signed rank test were used to compare parametric and nonparametric values, respectively, before and after each therapy and the relative changes in values in response to each therapy. The effects of tadalafil administration on vascular function, plasma levels of ET-1, VCAM, ICAM and insulin levels were analyzed by one-way repeated measures analysis of variance (ANOVA) or Friedman repeated ANOVA on ranks. A P-value <0.05 was considered statistically significant.

Results

The clinical characteristics of study patients and their biochemical status at baseline are shown in Table 1. Twenty out of 22 non-consecutive patients met the inclusion criteria at screening visit, entered into and completed the study. One patient was excluded because of the presence of homozygosis for the thermolabile variant of the *MTHFR* gene, and another because of concomitant assumption of 3 g/day omega-3. Safety analyses included all enrolled subjects. The most frequent adverse events were dyspepsia, headache, back pain, pain and myalgia and were present in overall two out of 20 patients (10%) during both regimes. These adverse events are typically reported with PDE5i. There were no reports of abnormal vision or priapism in either group. No difference in endothelial function was detected between patients with organic

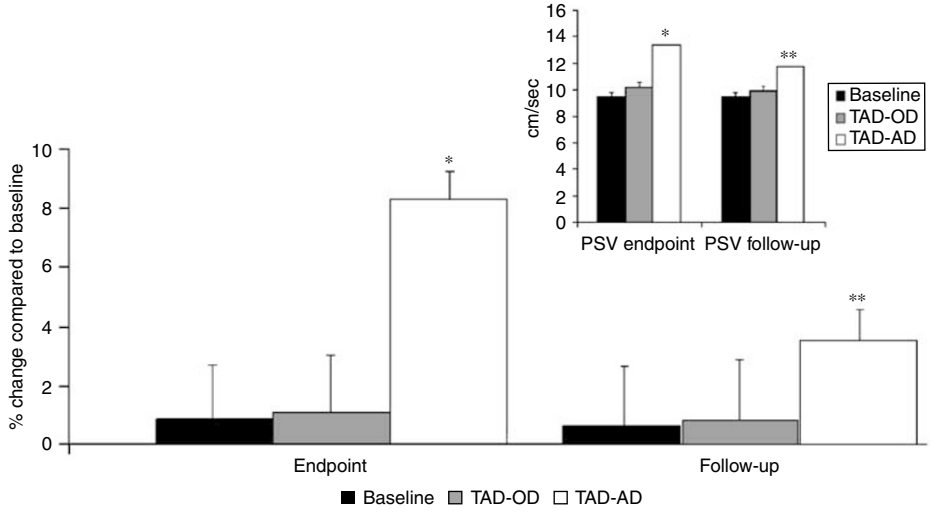

Figure 2 Percent change compared with baseline in endothelial function of cavernous arteries (FMD) in patients treated with TAD-AD and TAD-OD after 4 weeks of therapy and after 2 weeks of discontinuation of therapy. Inset indicates variations in cavernous arteries inflow as recorded by color-duplex ultrasound in the flaccid state. The P-values refer to comparison between end point vs baseline. $^*P<0.0001$; $^{**}P<0.005$.

or psychogenic ED (mean difference −0.1; range −0.6–0.5; patients with organic vs psychogenic ED).

Hyperemic diameters of cavernous arteries increased significantly after 4-week therapy with AD but not after OD (Figure 2). Changes from baseline in cavernous artery inflow (average of two sides) in the flaccid state were found after AD but not OD at both end point and follow-up of each treatment period, respectively (Figure 2, inset). Therefore, FMD increased significantly after AD but not after OD when compared to baseline and this benefit remained unchanged even after 2 weeks withdrawal of respective treatments (Figure 2). No clinically significant changes attributable to tadalafil in vital signs, that is, orthostatic hypotension, mean blood pressure or laboratory tests, were seen. In both treatment arms, the average dose used was 20 mg and the number of tablets assumed significantly differed between the two treatment periods ($P<0.05$), but no difference in the number of successful sexual intercourses per month and variations in blood pressure were reported at the end points (Table 2). No subject discontinued the medication owing to adverse events.

Table 2 Correlation between number of pills assumed and sexual intercourses per month compared to variation of blood pressure after different treatment regimes

	TAD-AD	*TAD-OD*	P-*value*
No. of pills/month	15.2±0.6	6.0±1.9	<0.05
Sex intercourse/month	6.0±0.7	5.9±0.4	NS
Systolic pressure (variation in mm Hg)	−4.0±1.3	−6.1±2.2	NS
Diastolic pressure (variation in mm Hg)	−2.3±1.2	−3.3±1.3	NS

Abbreviations: AD, alternate day; OD, on-demand; TAD, tadalafil.

Significant increases from baseline insulin levels were found in patients allocated to AD compared with those receiving OD (30 vs 10%, $P<0.05$) with concomitant decrease in CRP, VCAM and ET-1 levels (−35 vs −8%, −38 vs −5% and −18 vs −6%, respectively, $P<0.05$; Table 3, Figure 3). Concomitantly, also IMT decreased after AD when compared with OD and baseline, (from 0.066±0.002 to 0.061±0.005, NS and to 0.058±0.003 cm, $P=0.02$) and these benefits were sustained 2 weeks after withdrawal (from 0.066±0.002 vs 0.059±0.002 cm, $P<0.0005$ vs baseline; data not shown). Also, diameters of carotid arteries increased significantly after 4-week therapy with AD but not after OD ($P<0.05$, data not shown). Furthermore, improvement of morning erections was detected as evaluated by the Q13 of the SIEDY questionnaire: 'In the last four weeks, did it ever occur to you to wake up with an erection?', whereas almost all patients (90%) reported daily morning erections after AD compared to sporadic erections after OD regimes (Figure 4) that was maintained after 15 days withdrawal along with sexual satisfaction in intercourse (data not shown).

Discussion

The present study provides evidence, not previously reported, of an expected outcome that tadalafil on an AD dosing improves endothelial dysfunction and that these effects are also evident in other vascular districts, that is, carotid arteries, even after discontinuation of therapy. The improvement of endothelial function observed after continuous tadalafil administration may be owing to the modifications of biomarkers of endothelial function, that is, CRP, VCAM, ET-1 and insulin levels, as also confirmed by the IMT amelioration.

Table 3 Effect of tadalafil ADs versus OD on endothelial function

	Tadalafil-AD		*Tadalafil-OD*	
	Baseline	*End point*	*Baseline*	*End point*
Endothelial markers				
VCAM (ng/ml)	748.2±275.6	621.3±213.7*	720.5±277.1	705.1±285.2
ICAM (ng/ml)	273.1±75.5	280.6±69.5	270.1±80.3	268.6±69.5
ET-1 (pg/ml)	3.3±.2.1	2.6±1.9	3.0±1.8	2.8±2.7
CRP (mg/l)	3.1±0.4	2.4±0.2*	3.2±0.3	2.9±0.3
Insulin (mIU/l)	6.9±0.4	9.5±0.2*	6.8±0.6	7.2±0.5
Cavernous artery diameter				
Basal-1 (mm)	2.46±0.22	2.67±0.16*	2.41±0.24	2.39±0.23
Hyperemia (mm)	2.49±0.21	2.85±0.15*	2.43±0.25	2.67±0.19
FMD (%)	1.2±0.6	8.3±0.3*	3.3±0.6	2.1±0.9
PSV (cm/s)	9.5±0.4	13.2±0.1*	9.3±0.3	10.4±0.9

Abbreviations: AD, alternate day; CRP, C-reactive protein; ET-1, endothelin-1; FMD, flow-mediated dilatation; ICAM, intercellular cell adhesion molecule; OD, on-demand; PSV, peak systolic velocity of the cavernous artery (average of two sides); VCAM, vascular cell adhesion molecule.
Data are expressed as means±s.d.
*$P<0.05$ versus respective baseline value.

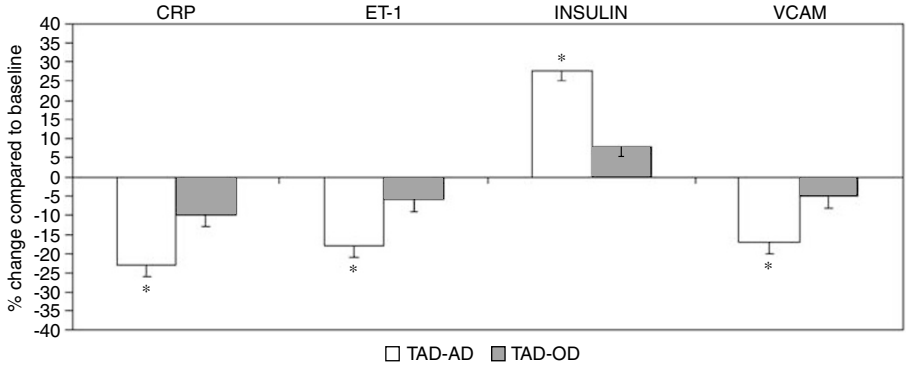

Figure 3 Percentage changes in plasma levels of markers of endothelial function in patients treated with TAD-AD compared with TAD-OD at end points. *$P<0.05$.

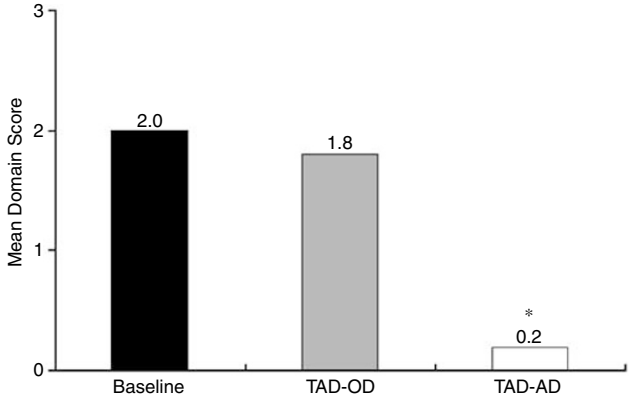

Figure 4 Effects of different regimes of tadalafil on morning erections reported by the patients as expressed by the Q13 of the SIEDY questionnaire scores: 'In the last four weeks, did it ever occur to you to wake up with an erection?'. *$P<0.0001$ vs baseline and vs OD.

The endothelium is involved in numerous physiologic functions, such as the regulation of vascular tone and permeability, the maintenance of equilibrium between coagulation and fibrinolysis, and the proliferation of smooth muscle cells.[14] Vascular endothelium produces a variety of regulatory mediators which reflect vascular inflammation and oxidative stress; VCAM seems to play a critical role in triggering of atherosclerosis. In addition, recent observations suggest that insulin also acts as an anti-inflammatory hormone[15] and treatment of type II diabetes with insulin for 2 weeks causes a reduction in CRP and monocyte chemotactic protein-1.[16] Consistent with this finding, Stentz *et al.*[17] showed that treatment of severe hyperglycemia associated with marked increase in inflammatory mediators with insulin resulted in a rapid decrease in the concentration of inflammatory mediators. According to previously published data,[18] in the present study, we have shown that administration of tadalafil every other day improves FMD of cavernous arteries mostly in patients with ED owing to arterial origin, thus confirming data obtained in the study of Rosano *et al.*[10] carried out on brachial arteries. A possible explanation of sustained improvement of endothelial function after discontinuation of chronic tadalafil therapy may be related to the recent finding that PDE5i administration produces a sustained increase of circulating progenitor cells over the time.[19] This finding, even if needing further confirmation, may have important implication for the potential role of PDE5i in the prevention and progression of cardiovascular diseases. Furthermore, alternative mechanisms involved in the effects of tadalafil may be also related to its documented cardio-protective effects, which are supposed to be mediated by the *akt*-signaling pathway activation[20] which leads to endothelial nitric oxide synthase activation and that have not been investigated in this study. Another possible explanation may be dependent on the inhibitory effect of tadalafil on cyclic 3′,5′ guanosine monophophate degradation at the endothelial level with consequent increase in insulin secretion, as previously reported by other authors'.[21] At present, the effect of PDE5 inhibition on endothelial function remains controversial; animal studies in hypercholesterolemic[22] and diabetic[23] rat models suggest that this class of drugs may be effective in improving the degree of induced endothelial dysfunction; on the other hand, studies in humans suggest that this does not improve peripheral endothelium dependent vasomotor or fibrinolytic function in patients with coronary heart disease.[24]

The results of this study have important clinical implications for patients with impaired endothelial function regardless of the presence of clinical cardiovascular disease,[25] and for this reason our study population included tadalafil responders only, no matter their ED etiology so that we did not perform a complete diagnostic workup before entering into the study. Previous epidemiological studies have demonstrated a close relationship between ED and cardiovascular disease and suggested the hypothesis that vascular ED may be an early marker of cardiovascular disease.[26] Montorsi *et al.*[27] have reported that in 70% of men undergoing

coronary angiography, ED preceded the clinical manifestations of coronary artery disease. Kim *et al*.[28] have reported a 56% incidence of positive exercise tests in men with vascular ED and without any cardiovascular symptom and have found significant atherosclerosis at angiography in all those patients who underwent coronary angiography. Similar findings were reported in men with ED and low peak flow velocities at penile Duplex ultrasound.[29] Altogether, these findings suggest that the endothelial dysfunction, which is a marker of early stages of atherosclerosis, has an impact on erectile function both in organic and psychogenic patients[30] being the penile circulation mainly dependent upon correct endothelial function and less on metabolic-induced vasodilation. Indeed, in accordance with the data previously reported by Mancini*et al.*,[31] our patients showed pathological baseline PSVs at Duplex ultrasound that were consistent with the presence of endothelial dysfunction in almost all of our patients; a significant amelioration after ADs tadalafil administration with parallel improvement of penile FMD after shear stress occurred. These results are in line with recent studies on the role of PDE5 inhibition in improving endothelium-dependent vasodilation, that is, pulmonary hypertension, primary hypertension and heart failure, conditions in which sildenafil has been shown to improve pulmonary pressures as well as functional capacity.[32] Even if our data have been clearly obtained in a low number of patients compared with those with statins or ACE inhibitors,[33] they are very encouraging in that they provide further knowledge demonstrating that PDE5 inhibition is able to restore impaired endothelial function of cavernous arteries.[18]

The reduction or absence of nocturnal erectile episodes has been reported as a possible mechanism in the pathogenesis of ED.[34] The consequent reduction in the environmental oxygen tension to which cells are exposed leads to physiological and, eventually, pathological consequences associated with differential expression of specific genes that encode for cytokines and growth factors thought to play key roles in the regulation of synthesis and assembly of connective tissue proteins, that is, transforming growth factor-β1 and pltelet-derived growth factor,[35] which are overexpressed in tunica albuginea from men suffering from venocclusive dysfunction[36] and in plaques obtained from Peyronie's disease.[37] Reports on the improvement of morning erections after short-acting PDE5i assumption is frequent if the drug is taken daily at bedtime[38] but this effect is lost after 2 or 3 days of withdrawal. Accordingly, in this study, also OD tadalafil administration did not improve morning erections reported by the patients as opposed by a dramatic change occurring after ADs administration, which was maintained within 15 days after withdrawal. This suggests a possible rehabilitative action of tadalafil that might be exerted through an inhibition of expression of intrapenile pro-fibrotic growth factors determined by chronic hypoxia and absence of nocturnal tumescence episodes.

In conclusion, chronic not OD therapy with PDE5i tadalafil improves endothelial function in men with several ED etiologies. This may sometimes represent the preferred therapeutic scheme in up to 42% of treated patients in multicenter studies comparing different regimes.[39] Moreover, current available data suggest that also a once-a-day 5 or 10 mg dosing may be well tolerated and significantly improves erectile function in men with ED.[40] We are aware of the caveats of this study, lacking a placebo arm which might have demonstrated effectiveness in improving endothelial responsiveness in patients with vascular impairment.[10] However, based on data obtained in previous studies, which clearly failed to demonstrate any beneficial effect of PDE5i in improving endothelial function of healthy men,[41] we hypothesize that in our series of patients with co-morbidities, that is, diabetes, hypertension, hypercholesterolemia, tadalafil represented a consistent addiction to the vascular effects of other therapies. Finally, improvements of morning erections may provide better end-organ oxygenation and erectile function rehabilitation when compared to OD use. This is a confirmatory study, which suggests that larger controlled multicenter studies involving representative populations for longer duration periods and follow-up after withdrawal should be encouraged.

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