

Redefining the Role of Long-Acting Phosphodiesterase Inhibitor Tadalafil in the Treatment of Diabetic Erectile Dysfunction

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Abstract: Diabetes mellitus (DM) is an established risk factor predisposing to male erectile dysfunction (ED), and it has been calculated that more than 50% of diabetic men develop ED within ten years of diagnosis. It has been suggested that the risk of ED increases with metabolic indices of inadequate diabetes control and with a longer duration of disease. Loss of the functional integrity of the endothelium and subsequent endothelial dysfunction plays an integral role in the pathogenesis of diabetic ED. Coronary and peripheral atherosclerosis are frequent complications of DM and diabetic patients have an increased risk of future cardiovascular events comparable to that of patients with coronary artery disease. The prolonged half-life of tadalafil (17.5 hours) and its prolonged period of responsiveness (36-hours), constitute an ideal pharmacokinetic profile for once-a-day dosing and makes it an ideal candidate for rehabilitative therapy in DM patients, whereas a poor compliance with on-demand schedule is reported.

The aim of this review will be to give an update on clinical overall efficacy and safety of tadalafil trials, i.e. in diabetic population, and finally provide evidences for redefining the role of chronic treatment in selected group of patients.

Keywords: Endothelial dysfunction, Phosphodiesterase type-5 inhibitors, Diabetes mellitus, Cardiovascular disease, Once-a-day dosing.

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability of a man to attain and/or maintain a penile erection sufficient for sexual performance [1].

In the new millennium, male ED often represents the “tip of the iceberg” of a systemic vascular disorder; about 50–85% of ED patients is estimated to have an organic cause by modern methods of examination [2]. Many diseases which are commonly encountered in the aging male (diabetes, metabolic syndrome, hypogonadism, hypertension, atherosclerosis, cardiovascular and neurological disease) as well as chronic diseases (arthritis, renal and hepatic failure, pulmonary disease) represent a frequent cause of organic ED and are often treated with medications that can interfere with sexual function at central and/or peripheral level. In addition, incorrect lifestyle – i.e. high fat meals, cigarette smoking, alcohol or drug abuse – may all contribute to the onset of ED. It is now well understood that male ED is a symptom of specific, systemic or relational pathologies rather than a disease itself; for this reason in the near future both general practitioners and specialists in internal medicine would have to interplay with sexual medicine. ED may constitute the first manifestation of important systemic pathologies and is considered as a possible marker of atherosclerotic, metabolic and neurological pathologies which remain clinically undiagnosed. ED is more common in men with diabetes mellitus (DM) and is often associated with vascular disease. Coronary and peripheral atherosclerosis are frequent complications of diabetes. Patients with DM have an increased risk of future cardiovascular events comparable to that of patients with coronary artery disease (CAD) [3, 4]. Therefore, regarding the risk of cardiovascular events, DM can be considered equivalent to established CAD [5]. The incidence of DM is increasing at an alarming rate, and diabetic men already make up a quarter of the men in the overall population of ED. As already outlined, impotence occurs in almost 50% of men with DM, and the rate of sexual dysfunction is only slightly lower in diabetic women [1]. The onset of ED occurs at an earlier age in patients with DM. In more than 50% of patients with ED and DM, the former is noted within ten years of the onset of DM; it may present as the first sign of diabetes in as much as 10% of patients [6]. Temporary ED may be due to poorly controlled diabetes, although this point is debatable. ED seems to occur at an earlier age in type-1 than in type-2 diabetic patients, although probably occurs

with equal frequency in the two types. Ageing, cigarette smoking and the presence of diabetic complications (neuropathy, vascular diseases, retinopathy and nephropathy) show a significant relationship with the occurrence of ED in both type-1 and type-2 diabetes [7].

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; also, endothelial function is impaired in patients with overt atherosclerotic disease as well as in those at increased cardiovascular risk and it is often present in diabetic patients even without clinically evident atherosclerotic diseases [8, 9]. In addition to blunted endothelium-dependent and -independent responses diabetic patients are reported to have a reduced response to vasoactive agents [10].

The recent discovery that chronic, not on-demand administration of phosphodiesterase type-5 inhibitors (PDE5-i) may improve erectile and endothelial response in men previously unresponsive to on-demand regimes, opens a new scenario in the treatment of men with ED and comorbidities. PDE5-i are a group of on-demand drugs licensed for ED treatment and appear to offer advantages over past therapies in terms of ease of administration and cost, and they are now widely advocated as first-line therapy. These drugs have been shown to improve erectile function, penetration and maintenance of erection, resulting in more successful intercours. Sildenafil and vardenafil are short-acting agents, while tadalafil has a longer half-life allowing the user more flexibility in sexual activity. Although the various classes of PDE5-i differ with respect to selectivity and pharmacokinetic profiles, efficacy and safety of these agents are comparable in broad populations of men with ED. PDE5-i facilitate erection by increasing nitric oxide (NO) availability through the inhibition of cyclic guanosine monophosphate (cGMP) breakdown in endothelial cells [11]. Efficacy of PDE5-i is reported to be lower in men with ED and DM compared with those without DM [12]. Similarly the endothelial effectiveness of drugs known to improve endothelial function is lower in patients with diabetes compared with patients without diabetes [13]. It has been suggested that chronic PDE5-i administration may regulate the transduction pathway leading to the activation of endothelial-NO synthase (eNOS) with no effect on NO bioavailability or on the cGMP pathway, thereby eliminating a possible concern for tachyphylaxis [14] and that chronic administration of PDE5-i may improve endothelial function long term [15].

Aim of the present article will be to review the efficacy and safety data of long-term therapy with tadalafil in patients with DM and to provide an up-date on endothelial function effects determined by its chronic use in this special sub-population of patients.

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PHARMACOKINETICS, EFFICACY AND SAFETY OF TADALAFIL

Tadalafil (Cialis®) is a potent, reversible, and selective PDE5-i recently approved worldwide as an oral therapy for mild-to-severe ED of psychogenic, organic, or mixed etiology [16]. The onset of action of tadalafil has been demonstrated at 16 to 30 minutes post-dose, but the feature that most distinguished tadalafil from its predecessors was its duration of action: with its mean terminal half-life of 17.5 hours, tadalafil has allowed couples to engage in successful intercourse up to 36 hours post-dose. Steady state is attained by day 5 following once-daily administration, and accumulation (1.6-fold) is consistent with the estimated $t_{1/2}$, thus suggesting that tadalafil neither induces nor inhibits its own metabolism [17]. The pharmacokinetic studies on tadalafil demonstrated that neither the consumption of a high-fat meal nor the timing of the dosing (morning or evening) have any effect on changes in plasma concentration or time to maximal response. These findings suggest that it can be administered at any time, with or without food, and regardless of the fat content of the meal, resulting in no effect on absorption [18]. Similarly, no interactions have been demonstrated between tadalafil and alcohol. There are pharmacological interactions between tadalafil (as all other PDE5-i compounds) and other medications metabolized by the cytochrome P450 system, being substrates of cytochrome P3A4 and metabolites of tadalafil are devoid of biological activity. Both drug and its metabolites are excreted in the feces [19]. Being potent inhibitors of the cytochrome P3A4, tadalafil may interact with other compounds that act as substrates/inducers of this cytochrome system, such as the HIV protease inhibitors (ritonavir, indinavir, etc) [20], the azole antifungals, erythromycin, etc., which lead to an increase in the systemic exposure of the PDE5-i of 2 – 16-fold. Cytochrome P3A4 inducers, such as rifampin, reduce the circulating levels of PDE5-i on the other hand [21]. Further attention should be made also in prescribing drugs interfering with cytochrome P3A4-metabolic pathway (e.g., statins) in order to avoid toxic effects. No consistent pattern of serious adverse events assessed as causally associated with tadalafil administration was observed. Caution should be exercised when prescribing these drugs together [22].

Tadalafil is absolutely contraindicated in patients taking nitrate or molsidomine-containing medications and it may interact in particular with non-uroselective α -adrenoceptor blockers. In a patient who has taken tadalafil, and in whom nitrate administration is deemed necessary in a life-threatening situation, a minimum of 48 hours should pass between dosing with tadalafil and administration of nitrates, which would be commenced only under close medical supervision and with appropriate haemodynamic monitoring [23, 24]. Recently, Kloner *et al.* evaluated the haemodynamic effects of doxazosin 8 mg with tadalafil 20 mg, and tamsulosin 0.4 mg with tadalafil 10 and 20 mg. Tadalafil 20 mg augmented the hypotensive effect of doxazosin by producing a mean maximal decrease in standing systolic blood pressure (SBP) that was significantly greater than placebo (a mean difference of 9.8 mm Hg). Analysis of blood pressure outliers showed that the number of subjects with a standing SBP of less than 85 mm Hg was greater after doxazosin plus tadalafil (28%) versus doxazosin plus placebo (6%). In subjects on tamsulosin, tadalafil 10 and 20 mg produced mean maximal decreases in standing SBP that were similar to placebo (mean difference of 1.7 and 2.3 mm Hg, respectively). No subject taking tamsulosin had a decrease in standing SBP less than 85 mm Hg. These results show that Tadalafil may increase the hypotensive effects of doxazosin but have little hemodynamic interaction with tamsulosin. In patients taking tadalafil for ED, tamsulosin 0.4 mg may be given for the treatment of benign prostatic hyperplasia [25].

The occurrence of QT interval prolongation (more evident after vardenafil administration) even in the absence of onset of malignant arrhythmias, suggests caution in special population such as patients assuming concomitant drugs interfering with adrenergic and cholinergic neurotransmission (e.g., antidepressants, alpha-lithics). The

second Princeton Consensus Conference has highlighted the relation between ED and cardiovascular disease, stratifying ED patients in three risk classes. Low risk patients could immediately initiate a treatment for ED without further cardiac evaluation; patients with intermediate or indeterminate risk should be clinically evaluated and reclassified as high or low risk patients; high risk patients should defer resumption of sexual activity until cardiological assessment and specific treatment has been defined [26].

The adverse events associated with tadalafil use are generally mild-to-moderate and decrease in frequency with continued administration. In a study of 18 months duration and involving 1173 men with ED, the study drop-out rate was 6.3% with a rate for any individual event of <1%. Headache (15.8%), dyspepsia (11.8%), nasopharyngitis (11.4%), and back pain (8.2%) were the most common treatment-emergent adverse events [27]. Priapism and prolonged erection are rare adverse events that have been reported with this class of drugs. There were no clinically significant laboratory or ECG findings or changes in vital signs in mean baseline-to-endpoint analysis attributable to tadalafil [28].

Changes in color vision have been very rare (<0.1%) with tadalafil across all clinical trials [29]. Infact, most classes of PDE inhibitors inhibit the photoreceptor PDE6 isoform rather well, similarly to the PDE family to which they were targeted, i.e., PDE5 in this case. In intact rod outer segments, high PDE6 concentrations are present, and the binding of inhibitors to the gamma-subunit to the active site, and calcium feedback mechanisms attenuate the effectiveness of PDE inhibitors, leading to inhibition of PDE6, disruption of the cGMP signaling pathway during visual transduction, and some transitory visual side effects of this entire class of drugs [30]. Therefore, there have been several case reports suggesting a link between sildenafil [31] and, tadalafil [32] also, and non-arteritic anterior ischaemic optic neuropathy (NAION). Visual side effects (for example, light sensitivity, colour vision abnormalities) associated with these medications are well documented but these effects, which have been traced to the fact that PDE5-i appears to have an inhibitory influence, albeit weak, on enzymatic activity in the rod and cone cells, appear to be transient in nature [33]. However, the mechanism by which these medications might damage the optic nerve is not as well understood. It has been theorised that sildenafil, which works through the NO/cyclic/GMP pathway, may alter the perfusion of the optic nerve head by modifying NO levels [34]. Given their similar properties, it can also be theorised that tadalafil might act similarly though no explicit theories have been proposed. Unfortunately, to date there is no empirical evidence for or against an association between tadalafil and NAION. Hypertension and diabetes also predispose to NAION development [35]. Other risk factors that have been hypothesised to associate with NAION include high cholesterol, arteriosclerosis, stroke, cardiac and intraocular surgery, tobacco use, nocturnal hypotension, blood loss, glaucoma, elevated homocysteine and sleep apnea. The association between NAION and hypertension, high cholesterol and diabetes is stronger in individuals younger than 50 years than in older persons [36]. Many of the risk factors for developing NAION also predict the occurrence of ED, such as hypertension, diabetes, hyperlipidemia and smoking [37, 38]. NAION has been reported rarely in men after taking sildenafil or other PDE5-i for ED. The incidence of NAION in men receiving sildenafil treatment for ED was estimated using pooled safety data from global clinical trials and European observational studies. Based on clinical trial data in more than 13,000 men and on more than 35,000 patient-years of observation in epidemiologic studies, an incidence of 2.8 cases of NAION per 100,000 patient-years of sildenafil exposure was estimated. This is similar to estimates reported in general US population samples (2.52 and 11.8 cases per 100,000 men aged ≥ 50 years). The data cited herein do not suggest an increased incidence of NAION in men who took sildenafil for ED [39].

Myalgia and back pain are two of the most common adverse event reported with tadalafil and the cause has been recently investi-

gated. Cross-reaction with proteins other than PDE5 would suggest the potential for such side effects and PDE11 is an obvious candidate for this role since it is closely related to PDE5 and expressed also in skeletal muscle. The amino-acid sequence of the catalytic domain of PDE11 is approximately 51% identical with that of the catalytic domain of PDE5, suggesting the possibility that commercially available PDE5-i might cross-react with PDE11. Weeks *et al.* investigated this hypothesis comparing the biochemical potencies of tadalafil, vardenafil and sildenafil for PDE11A4 and PDE5A1. The results obtained seem to exclude definitively any cross reaction for sildenafil (1000-fold selectivity) and vardenafil (9000-fold selectivity) but also tadalafil selectivity (40 fold) makes it unlikely a cross reaction with PDE11A4 [40]. Further studies investigated potential serious causes for these side effects including muscular trauma/damage, abscess, inflammatory processes, myositis, vasculitis, fasciitis, rhabdomyolysis, venocongestion, or kidney pathology. The results of these studies did not support any of these serious causes so the mechanism underlying this phenomenon remains unknown [41]. Anyway, in our opinion this should not affect the profile of safety of PDE5-i considering that the symptoms are self-limited and no evidence of injury to the muscles or kidneys has been found.

Recently, the US Food and Drug Administration warned that sudden loss of hearing in patients taking PDE5-i may occur. It was based on 29 postmarketing cases that occurred in a strong temporal relationship to dosing with sildenafil, tadalafil and vardenafil. In some cases, the sudden loss or decrease in hearing was accompanied by vestibular symptoms such as tinnitus, vertigo, and dizziness. Hearing loss was temporary in about 33% of patients; for the remainder, hearing loss was either ongoing at the time of report or the final outcome was not described. In almost all cases, the condition was one-sided. Because follow-up information was often limited, it remains unclear whether these events were caused by medication use, underlying medical conditions, or a combination of these or other factors.

EFFICACY OF TADALAFIL IN DIABETIC ED: DAILY VS. ON-DEMAND DOSING?

Before analyzing the results obtained in diabetic populations, we report those regarding some independent studies which investigated once-a-day tadalafil in ED treatment of any origin. The first study tested tadalafil 10 and 20 mg as a 'salvage' therapy for patients who were unresponsive to tadalafil 20 mg on-demand. Erectile function with once-a-day therapy was significantly higher than baseline and compared with on-demand dosing [42] as assessed by IIEF (International Index of Erectile Function), SEP (Sexual Encounter Profile), and GAQ ('Global Assessment Question'). The second one, was aimed to compare on-demand tadalafil 20 mg with once-a-day tadalafil 10 mg. The mean change scores in erectile function from baseline was significantly higher for once-a-day (11.8 points) than for on-demand (8.7 points). Based on these results, once-a-day tadalafil may provide superior efficacy compared with on-demand. Furthermore, 72% of the study population preferred the former modality of assumption [43]. Because of the broad differences between McMahon's studies, direct comparisons cannot be made, but both studies show that patients respond well to once-a-day tadalafil. Hence, once-a-day dosing with tadalafil may be an attractive alternative to on-demand therapy especially for some patients who wish to resume spontaneity and naturalness in sexual activity as well as partner satisfaction [44].

Another important study aimed to compare tadalafil taken on-demand or three times per week, was the SURE-study carried out in the diabetic population with ED. The efficacy and safety of tadalafil in this subpopulation, which is considered by most to be difficult to treat, followed a pattern very similar to that of the overall SURE study population. In the SURE-study, the efficacy and safety of 20-mg tadalafil were evaluated in 4,262 patients with ED. Of these patients, 762 had type-1 or type-2 DM. In this study, patients were on the three-times per-week or on-demand treatment regimen for a short

time (5–6 weeks) before switching to the alternate treatment. The efficacy of 20-mg tadalafil in patients with ED and diabetes during this short treatment period was slightly higher, but not significantly, on the three-times-per-week regimen [45]. Tadalafil was well tolerated by patients with DM and ED with a pattern of adverse events in both treatment regimens similar to that in the overall SURE-study population. The pattern of sexual attempts among patients with DM was similar to the overall SURE-study population [46]. More than 70% of sexual attempts while on the three-times-per-week regimen and approximately 50% of the attempts on the on-demand treatment occurred more than 4 hours post-dosing. This pattern of sexual attempts indicates that, as in the overall SURE-study population, the subpopulation of patients with DM used the wide duration of efficacy of tadalafil. As in the overall SURE-study population, more patients in the diabetes subgroup (57.2%) preferred taking 20-mg tadalafil on-demand, but a substantial number (42.8%) preferred three times per week [47]. Response to tadalafil treatment in men with DM has been robust and not affected by disease severity. After 12 weeks of therapy, the patients (64%) receiving 20 mg and the patients (56%) receiving 10 mg reported positive responses to a GAQ regarding improved erections versus patients (25%) receiving placebo. Moreover, men who received tadalafil were also more likely to have an increase of more than 5 points in the IIEF-EF domain score than patients in the control group. An increase of this magnitude with an improvement from severe to moderate ED (a score of 18), is clinically noteworthy when considered in a population of men who are likely to have longstanding and fairly advanced diabetes [48]. A study from Forst and co-workers demonstrated that daily administration of tadalafil 5 and 10 mg is efficacious and well tolerated with mean erectile function domain scores increased by 9.7 (tadalafil 5 mg) and 9.4 points (tadalafil 10 mg). Adverse events reported by patients tended to be mild or moderate in severity, and the rate of discontinuations caused by adverse events was similar to rates seen in studies that used on-demand dosing [49]. Since controlled studies in diabetic population are lacking, a randomized, double-blind, placebo-controlled, multicenter, 12-week study has been recently carried out to evaluate the efficacy and tolerability of daily dosing with tadalafil 2.5 mg and 5 mg by men with ED and DM. Results showed that Tadalafil 2.5 mg and 5 mg taken once daily significantly improved erectile function for all co-primary endpoints. Mean changes in IIEF EF Domain scores were 4.8, 4.5 and 1.3 (tadalafil 2.5 mg, 5 mg, and placebo, respectively). Also, significant changes were reported in SEP when compared with placebo so that it was concluded that tadalafil significantly improved overall treatment satisfaction [50].

Finally, a recent retrospective analysis of data from placebo-controlled and open-label clinical trials of Tadalafil with as needed, three times-per-week or once-a-day dosing and having ≥ 1 of the cardiovascular risk factors of hypertension, diabetes, obesity, smoking, and age > 65 years, showed that the incidence of serious cardiovascular treatment-emergent adverse events was comparable between tadalafil- and placebo-treated patients. In patients with ≥ 2 of the risk factors of hypertension, diabetes, and hyperlipidemia, the incidence rate of serious cardiovascular treatment-emergent adverse events ranged from 0.98 to 2.55/100 patient-years in tadalafil-treated patients (open-label and placebo-controlled trials, respectively) compared with 2.21/100 patient-years in placebo-treated patients. Although the incidence rates were comparable between tadalafil- and placebo-treated patients with cardiovascular risk factors, as expected, the incidence rates in these patients were higher than in the overall clinical trial population [51].

BEYOND ED: EFFECTS ON ENDOTHELIUM, CARDIOVASCULAR SYSTEM AND SEX STEROIDS

An emerging role in the management of ED seems to be the chronic use of PDE5-i with a threefold purpose: 1) recovering non responders to on demand therapy; 2) rehabilitation of erectile function which means endothelial rehabilitation and 3) modification of hor-

Table 1. Sexual and Extrasexual Effect of Chronic Tadalafil Administration in Clinical Trials

System	Effect	Adverse Events	Reference
Penile	Improvement in penile vascular circulation and resumption of morning erections	None	Proietti M. J Rheumatol 2007; 34(8): 1712-7
Vascular endothelium	Decrease pro-atherogenic markers Increased NO availability Rehabilitation	None	Rosano GM. Eur Urol 2005; 47(2): 214-20
Heart	Cardio-protection Myocardial remodelling Favorable safety profile	Delayed nitrate administration for MI	Kukreja & Salloum. Int J Impot Res 2007; 19(2): 226-7
Eye	Improvement of microcirculation	Change in color vision (<0.1%) NAION	Padma-Nathan H. Am J Cardiol 2003; 92: 9M-25M
Ear-Nose-Throat	Not known	Hearing loss	MedWatch FDA, 2007
Endocrine	Increase T and T:E ratio	None	Greco EA. J Sex Med 2006; 3(4): 716-22
Pulmonary	Reduction of pulmonary pressure	None	Mukhopadhyay S Circulation 2006; 24(114): 1807-10
Prostate	Improvement of LUTS in BPH	None	McVary KT. J Urol 2007; 177: 1401-7
Metabolic	Improvement of insulin release	Not known	Aversa A. Int J Impot Res 2007; 19(2): 200-7
Liver	None	Interaction with medications metabolized by the cytochrome P450	Ring BJ. Clin Pharmacol Ther 2005; 77(1): 63-75
Skeletal muscle	No improvement in exercise capacity	Myalgia and back pain	Di Luigi L. Int J Sports Med 2007; 5: [Epub]
Bone marrow	Increases of EPC	Autonomous cell Proliferation?	Foresta C. Int J Impot Res 2006; 18(5): 484-8

Legends: NAION= Non-arteritic Anterior Ischaemic Optic Neuropathy; MI=myocardial infarction; EPC=endothelial progenitor cells; LUTS=lower urinary tract symptoms; BPH=benign prostatic hyperplasia; T=testosterone; E=estradiol.

monal patterns (Table 1). As already outlined, two separate studies demonstrated a significant enhancement in all efficacy outcome variables after receiving tadalafil daily (10 mg) compared with on-demand regimes in non-diabetic men with ED [42, 43]. These results were achieved preserving the good profile of safety and tolerability of this PDE5-i, with a similar incidence and severity of adverse events with respect to on-demand tadalafil treatment with the exception of headache, which was less common with daily tadalafil 10 mg than with on-demand tadalafil and a rate of treatment discontinuation due to intolerable adverse events of 2.7%. Rosano & Aversa evaluated whether scheduled tadalafil (every-other-day for 4 weeks) might improve endothelial function in patients with increased cardiovascular risk, which is a broad population sharing similar risk factors with diabetic population. They found that brachial artery flow-mediated dilation (FMD), nitrite/nitrate and endothelin-1 plasma levels significantly improved in treated vs. placebo groups and were maintained after 2 weeks from withdrawal [15]. Additional data on endothelial response to chronic tadalafil have been obtained from the same researchers in a small number of men with ED and co-morbidities [52]. Altogether, results suggest a beneficial effect on endothelial function via decreasing plasma levels of surrogate markers, i.e. endothelin, CRP, VCAM. In their study, the authors added another possible mechanism underlying penile rehabilitation, that is improvement of morning erections, which may provide better end-organ oxygenation especially in diabetic population. This latter aspect was confirmed in another study carried out in male sclerodemic patients with ED by

Proietti&Aversa [53]. In that study, besides improvement in penile vascular circulation, daily tadalafil determined marked reduction of endothelin-1 plasma levels as well as resumption of morning erections after 12-weeks of treatment. Although this appear to be a fascinating hypothesis which opens new treatment perspectives, it is our opinion that larger studies are needed in order to assess the possible clinical implications of chronic therapy with tadalafil on both cardioprotection and endothelial rehabilitation in patients with DM. To support this latter aspect, in a recent animal study, it was found that experimental diabetes was accompanied by a decrease in the smooth muscle and endothelial cell content, and the associated TGF- β 1 overexpression, eventually resulting in a decrease in the intracavernous pressure. These changes were all ameliorated by the subchronic treatment with a second generation of PDE5-i, DA-8159. These results suggest that the subchronic treatment can partially prevent the development of ED experimentally induced by streptozotocin administration, providing a rationale for the potential use of long-acting PDE5-i for treating ED secondary to diabetes mellitus [54]. Endothelial progenitor cells (EPCs) have been shown to provide an endogenous repair mechanism to counteract detrimental risk factor-induced effects and replace dysfunctional endothelium. The number and *in vitro* function of EPCs is altered in patients with heart failure and ED, as a result of its pathophysiological mechanisms. EPCs could represent a substitutional marker to guide preventive or therapeutic interventions in these diseases. Enhancing the number and functional capacity of EPCs with chronic tadalafil administration may elicit functional improvement in indi-

viduals with ED [55]; however, the exact role of EPCs enhancement in heart failure and potential therapeutic implications of tadalafil still remain to be elucidated.

Cardiovascular disease and ED share similar risk factors and often occur concomitantly due to either common etiology or pathophysiology (endothelial dysfunction). Therefore, men with ED may be at increased risk for cardiovascular adverse events and ED may be considered as a sentinel symptom in patients with occult cardiovascular disease. A recent, prospective, blinded, randomized controlled trial has shown that ED is a harbinger of cardiovascular clinical events in men aged 55 or over since older men had a 2-fold greater risk of cardiovascular disease than men without ED, thus recommending prompt investigation and intervention on cardiovascular risk factors [56].

An integrated analysis of cardiovascular adverse events was carried out with a dose range of tadalafil of 2-25 mg, with the majority of patients receiving tadalafil 20 mg. The incidence of cardiovascular adverse events in patients receiving tadalafil was low and comparable to placebo. Tadalafil did not increase the rate of myocardial infarction or cardiac mortality compared with reported rates from epidemiological studies. This favorable cardiovascular safety profile for tadalafil is important, because men with ED commonly have cardiovascular disease and may seek medical therapy for ED [57].

The relationship between diabetes, the metabolic syndrome and androgen deficiency is complex. Male hypogonadism is generally characterised by abnormally low serum testosterone levels. Free testosterone levels begin to decline at a rate of 1% per year after age 40 years. It is estimated to affect between 19-34% of men over the age of 60 [58]. Cross-sectional studies have found that between 20% and 64% of men with diabetes have hypogonadism, with higher prevalence rates found in the elderly. Hypogonadism can be a risk factor for the development of diabetes and the metabolic syndrome through various mechanisms including changes in body composition, androgen receptor polymorphisms, glucose transport, and reduced antioxidant effect. Conversely, diabetes and the metabolic syndrome can be risk factors for hypogonadism through some similar but mostly distinct mechanisms, such as increased body weight and leptin levels, decreased sex hormone binding globulin levels, suppression of gonadotrophin release or Leydig cell testosterone production, cytokine-mediated inhibition of testicular steroid production, and increased aromatase activity contributing to relative estrogen excess [59]. Defects in the hypothalamic-pituitary-gonadal axis may also result from type-2 DM, visceral obesity (which is strongly associated with insulin resistance), coronary artery disease and metabolic syndrome and from treatments with a wide range of medications [60]. Androgen deficiency can also occur at any time during a man's life, but occurs more frequently with advancing age (LOH, late onset hypogonadism).

Short-term interventional studies have also demonstrated that testosterone replacement therapy produces an improvement in insulin sensitivity in men. Thus hypotestosteronaemia may have a role in the pathogenesis of insulin-resistant states and androgen replacement therapy could be a potential treatment that could be offered for improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity and reduction in cardiovascular risk, particularly in diabetic men [61].

The role of testosterone salvage in the setting of 'sub-clinical' hypogonadism of patients with ED has to be assessed again in the presence or absence of PDE5-i effectiveness [62]. Basic studies have demonstrated that androgen deprivation decreases PDE type-5 expression in the human penis with a related reduction in protein expression [63]. It is likely that the efficacy of PDE5-i is blunted in patients with sub-clinical hypogonadism in whom androgen levels have not previously normalized [64]. Randomized controlled trials evaluating the effect of androgen replacement therapy on clinical response to PDE5-i are not yet available, but pilot studies have dem-

onstrated that androgen supplementation in diabetic androgen deficient men, restores the clinical response to PDE5-i [65].

As far as hormonal steroid pattern regards, there are several studies indicating that resumption of sexual function with different therapies is able to increase testosterone levels indirectly, through physiologic resumption of hypothalamic-pituitary pulsatility [66]. Further studies on different ED patients (including DM patients) demonstrated that tadalafil was superior to sildenafil in determining this effect [67]. Greco and co-workers disregarded that results by demonstrating that after long-term tadalafil treatment (12 months, with a mean of three tablets consumed per week) an increase of testosterone:estradiol ratio (decreased circulating estradiol levels) occurred through a reduction of estradiol levels, thus firstly hypothesizing an interplay between chronic tadalafil administration and aromatase activity [68]. The clinical impact of this newest action on male osteoporosis, breast and prostate cancer are under current investigation. Additional studies in chronic dosing with tadalafil are needed to determine its mechanism of action, identify patients who would benefit most from it, and evaluate its optimal duration of treatment.

CONCLUSIONS

ED is associated with the same underlying risk factors than vascular disease and include hypertension, hyperlipidemia, cigarette smoking, obesity, and aging. Diabetic patients have established endothelial dysfunction and are likely to have a greater incidence of adverse cardiovascular events than patients without risk factors and it is known that men with DM clinically asymptomatic for angina may display some degree of ED as their presenting symptom [69]. In this view, it is possible to hypothesize that precocious treatment of these men with daily tadalafil may represent a future strategy for preventing or reducing the extent of coronary dysfunction and/or myocardial infarction. Also, a daily-based approach may improve organic ED at the level of vascular endothelial function. Recent data suggest tadalafil could exert prolonged beneficial effects on vascular endothelial function if taken regularly [14, 15]. In our experience, endothelial response to tadalafil appears to be more prominent depending on the extent and degree of initial damage i.e. presence of systemic sclerosis or complicated diabetes, and suggests its potential use in preventing or slowing the progression of chronic disease complications. Taken together, data presented in this review suggest that once-a-day tadalafil administration is a safe and effective treatment in restoring erectile potency especially in men with diabetic ED (70% overall efficacy) in the long-term but does not provide evidence-based data on its capacity to improve endothelial dysfunction. In this view, once-a-day dosing with tadalafil should be an attractive alternative especially for those ED patients with overt endothelial dysfunction. As a part of the researchers involved in most important pilot studies regarding continued use of tadalafil in chronic diseases (i.e. diabetes and scleroderma), we believe that this drug fulfils all requisites for being introduced into clinical practice with the indication of daily dosing, due to its promising rehabilitative effects of both endothelial and erectile function. Post-marketing surveillance is necessary to provide further data regarding efficacy and safety in special populations.

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