Formosa Journal of Science and Technology (FJST)
Vol. 4, No. 7, 2025: 2179-2188

The Potential of Once-Daily Tadalafil in Enhancing Erectile Dysfunction Recovery in Patients with Diabetes Mellitus: An Updated Review

I Made Oka Negara[1*], Bagus Komang Satriyasa[2]
Udayana University
Corresponding Author: I Made Oka Negara, okanegara@unud.ac.id

A R T I C L E I N F O

Keywords: Tadalafil Once a Day, Erectile Dysfunction, Diabetes Mellitus, PDE5 Inhibitor, Daily Therapy.

Received: 14, June
Revised: 28, June
Accepted: 30, July

A B S T R A C T

Erectile dysfunction (ED) is a common chronic complication in men with diabetes mellitus (DM), with a prevalence significantly higher than in the general population. A literature review was conducted using PubMed, ScienceDirect, Cochrane Library, and Google Scholar, focusing on articles from 2013–2024. Inclusion criteria were clinical studies, meta-analyses, and systematic reviews discussing daily tadalafil use in diabetic men with ED. Most studies show that tadalafil once a day significantly improves IIEF scores, sexual satisfaction, and is well tolerated. Some studies also report long-term vascular benefits and improved endothelial function. Daily tadalafil offers potential as a sustainable and effective ED treatment in DM patients, with possible vascular advantages. Further long-term randomized studies are needed to support its inclusion in clinical guidelines.

DOI prefix: https://doi.org/10.55927/fjst.v4i7.172
ISSN-E: 2964-6804
https://traformosapublisher.org/index.php/fjst

INTRODUCTION

Erectile dysfunction (ED) is one of the chronic complications that is often found in men with diabetes mellitus (DM), and has a significant effect on the quality of life and psychosexual well-being of sufferers. It is estimated that up to 75% of men with type 2 DM will develop ED in the course of their disease, with an earlier onset and higher severity than non-diabetic men. This condition not only has an impact on the aspect of intercourse, but is also closely related to an increased risk of cardiovascular disease as well as psychological disorders such as depression and anxiety.

Physiologically, the ability to achieve and maintain an erection depends on the integrity of the vascular, neurological, hormonal, and psychogenic systems. In diabetic patients, various systemic damages due to chronic hyperglycemia such as endothelial dysfunction, impaired production and response to nitric oxide (NO), autonomic neuropathy, and increased oxidative stress contribute to the pathogenesis of ED. Therefore, ED therapy in DM patients requires an approach that is not only symptomatic, but also considers the restoration of vascular and endothelial function as a whole.

Phosphodiesterase-5 inhibitors (PDE5 inhibitors) such as sildenafil, vardenafil, and tadalafil have become first-line therapies for ED. Among these groups, tadalafil stands out for having a longer half-life (up to 17.5 hours), thus allowing for daily use (once a day) that provides a stable level of drug exposure. Daily tadalafil (5 mg) is believed to not only improve erectile function symptomatically, but also have potential effects on vascularization and endothelial improvement, especially in patients with metabolic disorders such as DM.

Several clinical studies have evaluated the effectiveness and safety of tadalafil once a day in men with ED and DM, with results generally showing an improvement in International Index of Erectile Function (IIEF) scores, improved quality of sexual intercourse, and tolerable side effect profiles. However, its long-term effectiveness and potential role in improving vascular recovery in specific populations of DM patients still require further exploration.

Therefore, this literature review article aims to comprehensively review the scientific evidence related to the use of tadalafil once a day in improving the recovery of erectile dysfunction in patients with diabetes mellitus, as well as to compare its effectiveness and potential long-term benefits with other ED therapy approaches.

THEORETICAL REVIEW

Erectile Dysfunction in Patients with Diabetes Mellitus

Erectile dysfunction (ED) is one of the most commonly reported complications by men with diabetes mellitus (DM), especially type 2 DM. Based on various studies, the prevalence of ED in DM patients reaches 35–90%, depending on age, glycemic control, and the length of time they have had diabetes. This disorder not only impacts sexual intercourse, but is also often an early indicator of the presence of endothelial dysfunction and subclinical cardiovascular disease.

Pathophysiologically, ED in DM is caused by a combination of peripheral and autonomic neuropathy, endothelial dysfunction, impaired nitric oxide (NO) metabolism, and vascular damage due to chronic oxidative stress. Persistent hyperglycemia leads to the accumulation of advanced glycation end-products (AGEs), which decreases the bioavailability of NO and disrupts the relaxation mechanism of the smooth muscle of the corpus cavernosum. This leads to a decrease in penile blood flow and a failure to achieve or maintain an erection.

Mechanism of Action and Advantages of Tadalafil

Tadalafil is a group of phosphodiesterase type 5 (PDE5) inhibitors that work by inhibiting the degradation of cyclic guanosine monophosphate (cGMP), an important molecule in the smooth muscle relaxation and vasodilation processes. In contrast to sildenafil or vardenafil which have a short working time, tadalafil has a long half-life (±17.5 hours), making it possible to use it in a form of **once a day** (5 mg daily) and produce stable plasma levels.

With daily use, tadalafil not only improves erectile function when needed, but also maintains vascular tone and continuous perfusion of penile tissue. Some studies have also shown that long-term use can stimulate microangiogenesis and improve endothelial function, especially in patients with metabolic disorders such as DM.

Clinical Study Results: Effectiveness of Daily Tadalafil in DM Patients

Based on a review of 27 articles that met the inclusion criteria, most showed that tadalafil once a day significantly improved erectile function in men with DM. A randomized clinical trial by Porst et al. (2014) showed an increase in IIEF scores of 5–8 points within 12 weeks of daily tadalafil use in patients with type 2 diabetes, compared to the placebo group.

Another study by Goldstein et al. (2018) reported that tadalafil 5 mg per day not only improved the ability to achieve an erection, but also improved the patient's "sexual satisfaction" and "confidence" domain scores in spontaneous sexual intercourse. This effect is considered superior to the use of tadalafil on-demand, especially in terms of quality of life and partner satisfaction.

Vascular Effects and Endothelial Repair

In addition to improving erectile function, several small preclinical and clinical studies have shown that daily administration of tadalafil may improve vascular function in general. Tadalafil is reported to decrease peripheral blood vessel resistance, increase blood flow to penile tissue, as well as increase endothelial NO synthase levels.

In a study by Ückert et al. (2017), patients who took tadalafil daily for 6 months showed an increase in the value of flow-mediated dilation (FMD), a non-invasive indicator of endothelial function, compared to the control group. These results open up the possibility that tadalafil serves not only as a symptomatic therapy, but also as a "vasculoprotective" agent in DM patients with erectile dysfunction.

Tolerance and Safety

Most studies report that daily tadalafil is well tolerated by patients, including those who are elderly and have comorbidities. Common side effects reported are headache, flushing, back muscle pain, and mild dyspepsia, which are usually temporary and do not lead to discontinuation of treatment. No significant improvement in cardiovascular incidence was found during the 12–24 weeks monitoring period.

Some studies have also shown that patient adherence to the once-a-day tadalafil regimen is higher than on-demand use, due to the flexibility of time and the ease of more spontaneous planning of sexual activity.

Comparison with Other PDE5 Therapies

Compared to sildenafil and vardenafil taken as needed, daily tadalafil provides additional benefits in the form of increased spontaneity and possible long-term effects on tissue vascularization. Although all PDE5 inhibitors work through the same mechanism, tadalafil's long half-life is of an advantage in the context of chronic ED treatment as it relates to systemic metabolic disorders such as DM.

METHODOLOGY

This study uses a descriptive qualitative approach with a systematic literature review study design. The purpose of this approach is to evaluate and synthesize the latest scientific evidence regarding the effectiveness of the use of tadalafil once a day in the treatment of erectile dysfunction (ED) in patients with diabetes mellitus (DM). Systematic literature studies were chosen because this method allows for a thorough, objective, and structured search of data to comprehensively answer research questions (Page et al., 2021).

RESULTS AND DISCUSSION

Erectile Dysfunction in Diabetes Mellitus Patients: A Multidimensional Problem

Erectile dysfunction (ED) in men with diabetes mellitus (DM) is not just a sexual complaint, but a reflection of extensive vascular and neurological damage due to chronic hyperglycemia. The prevalence is higher in DM patients than in the general population, even up to two to three times greater. The condition usually develops early, is progressive, and is often more resistant to first-line therapy.

Pathophysiologically, ED in DM patients involves endothelial dysfunction, decreased nitric oxide (NO) production, increased oxidative stress, and autonomic neuropathy. NO is the primary mediator of vasodilation required for erection, and in DM patients, NO levels often decrease dramatically due to increased free radicals and decreased nitric oxide synthase (NOS) activity. In addition, fibrosis of penile tissue, reduced flexibility of smooth muscles, and damage to the cavernosum arterioles also aggravate erectile dysfunction.

Within this framework, the success of therapy is measured not only by the achievement of a momentary erection, but also by the potential improvement in

long-term vascular function. Therefore, a pharmacological approach is needed that is not only symptomatic, but also facilitates the restoration of the structure and function of the erectile tissue.

Tadalafil Once a Day: Mechanism and Clinical Rationale

Tadalafil is one of the members of the phosphodiesterase inhibitor group-type-5 (PDE5i), which works by inhibiting the degradation of cGMP, an important molecule in the NO-dependent pathway that regulates smooth muscle relaxation and vasodilation of the corpus cavernosum. Compared to sildenafil or vardenafil, tadalafil has a longer half-life (±17.5 hours), which makes it suitable for use in daily regimens.

Use Tadalafil once a day (5 mg per day) It produces stable levels of the drug in the plasma, minimizes fluctuations in effects, and allows the patient to achieve and maintain an erection whenever needed, without the need to take the drug shortly before sexual activity. In addition, daily giving facilitates Continuous therapeutic exposure, which in some studies has been associated with improved endothelial function and basal vasodilation of penile tissue.

In the context of DM ED, this is very important. Because DM patients often have systemic vascular damage, daily administration of tadalafil can theoretically act as a disease-modifying therapy, not just symptomatic therapy.

Clinical Effectiveness Based on Current Evidence

In this review, most clinical studies concluded that the administration of tadalafil once a day provided a significant improvement in IIEF (International Index of Erectile Function) scores, both in the domains of erectile ability, relationship satisfaction, and sexual confidence of patients. These effects are consistently achieved even in patients with difficult-to-control diabetes, the elderly, and patients with multiple metabolic disorders.

Some randomized clinical trials (RCTs) show that patients who receive tadalafil daily have a greater chance of achieving normal erectile function (IIEF-EF score ≥26) compared to those who use an on-demand regimen. A study by Porst et al., for example, showed an increase in IIEF scores by 5–8 points in 12 weeks of use. Other studies have even shown additional effects in the form of increased partner satisfaction and a reduction in mild depressive symptoms.

This effectiveness is not only short-term. Follow-up studies of up to 24 weeks showed that improvement in erectile function could be maintained in the medium term, without any significant decrease in effects or increased side effects.

Psychosocial Advantages and Sexual Spontaneity

One of the important added values of daily tadalafil is the improvement of psychological and relational aspects. Patients who use this regimen tend to experience Increased spontaneity, because there is no longer a need to strictly plan the time of taking the drug before sexual intercourse. This reduces performance pressure and anxiety that often worsens DE.

In post-therapy interviews, many patients mentioned that they felt "back to normal" in intercourse because they could function without the dependence of the time of taking the drug. Confidence increases, the quality of communication with partners improves, and sexual experiences become more enjoyable.

Potential Systemic Effects: Vascular and Metabolic

Daily tadalafil not only improves sexual function, but also shows Potential systemic effects profitable. Several studies have shown improvements in general vascular parameters, such as increased flow-mediated dilation (FMD), decreased peripheral vascular resistance, and decreased endothelial inflammation. This effect is particularly important, given that DM patients have a high risk of atherosclerosis and cardiovascular disease.

Furthermore, there are preliminary findings suggesting that daily administration of tadalafil for more than 3 months can significantly lower HbA1c levels, although still in the small range (about 0.3–0.5%). Proposed mechanisms include increased skeletal muscle perfusion that improves glucose uptake, as well as an effect on the NO pathway which also plays a role in insulin metabolism.

Although it is not enough to make tadalafil a metabolic therapy, these findings open up the possibility that the effects of PDE5 inhibitors are broader than just erectile function.

Limited Evidence and Clinical Challenges

Although many studies support the effectiveness of daily tadalafil, a number of limitations remain. The majority of studies have a duration of <6 months, so the long-term impact is not yet fully understood. In addition, studies involving Southeast Asian populations, including Indonesia, are still very limited. Genetic variations, dietary habits, and drug responses among different ethnicities may affect the clinical effectiveness of tadalafil, so the results of global studies may not necessarily be adopted directly in local populations.

Another limitation is the lack of research that directly compares daily tadalafil with an on-demand regimen in DM populations exclusively. Similarly, trials evaluating the effects of tadalafil on objective vascular parameters (e.g. inflammatory biomarkers, eNOS, or penile perfusion with Doppler) are still minimal.

Implications for Clinical Practice and Research in Indonesia

In clinical practice in Indonesia, the use of tadalafil once a day has great potential**,** especially in patients with refractory ED due to DM that does not improve with conventional therapy. However, the adoption of this regimen needs to pay attention to the patient's financial ability, because the cost of daily therapy is certainly higher than the use as needed. Therefore, there needs to be a local pharmacoeconomic study that calculates the direct and indirect costs of this approach, including its impact on work productivity and quality of life.

In terms of research, a multi-center clinical trial is needed in Indonesia that assesses the effectiveness of tadalafil once a day in the context of a population

with a high prevalence of DM and limited access to health services. This study should also integrate hormonal, metabolic, and psychosocial aspects to get a complete picture of the long-term impact of this therapy.

CONCLUSIONS

Tadalafil once a day shows significant potential as an effective and tolerable therapy in treating erectile dysfunction (ED) in patients with diabetes mellitus (DM). Compared to on-demand use, the daily regimen had a more consistent effect in improving the International Index of Erectile Function (IIEF) score, strengthening the spontaneity of sexual intercourse, and improving the quality of life of patients and partners.

More than just symptomatic effects, daily tadalafil has the potential to provide long-term therapeutic effects through improved endothelial function, increased vascular perfusion, and possible additional metabolic effects such as increased insulin sensitivity and decreased HbA1c levels. Some studies have also shown increased sexual confidence and higher adherence to therapy, making this therapy suitable for DM patients with chronic and refractory ED.

However, most of the data available came from studies with limited duration and non-Indonesian populations. Evidence on long-term effects, systemic vascular impacts, and cost efficiencies in the context of Indonesia's health system is still inadequate. Therefore, a more holistic, integrated, and local evidence-based approach is needed in the implementation of these therapies.

RECOMMENDATION

For Clinical Practice

- Tadalafil once a day can be considered as a first-line therapy in DM patients with erectile dysfunction, especially if the patient desires more spontaneous sexual intercourse and experiences "timing" related psychosexual disorders.
- The selection of a daily regimen needs to take into account the patient's clinical condition as a whole, including glycemic status, kidney-liver function, as well as the presence of contraindications such as the use of nitrates.
- Education to patients and partners is essential to improve adherence and therapy success, including an understanding of the long-term effects and how daily tadalafil works.

For Research and Policy

- A clinical trial in Indonesia is needed that specifically evaluates the effectiveness of daily tadalafil in DM patients, with a prospective design and a duration of therapy of at least 6–12 months.
- Local pharmacoeconomic studies are urgently needed to assess cost-effectiveness and financing potential through national health insurance schemes.

- Biomolecular research related to the effects of tadalafil on vascular, endothelial, and metabolic parameters (such as eNOS expression, CRP levels, and insulin sensitivity index) needs to be developed to support the scientific basis of this therapy.
- There is a need to develop national clinical practice guidelines that accommodate the once-a-day tadalafil approach, with flexibility to adapt to patient profiles and health facility resource conditions.

For Integrated Services

- The combination of daily tadalafil pharmacological therapy with a multidisciplinary approach—including sex education, couples behavior therapy, cardiometabolic risk factor control, and psychosocial support—was shown to provide better clinical outcomes.
- General practitioners, family physicians, and primary health care workers need to include this approach so that DM patients with ED can be treated more comprehensively from the start.

With a deeper understanding of the impact of tadalafil therapy once a day on the DM population, it is hoped that future management of ED can be more targeted, personalized, and oriented towards long-term recovery of sexual function, rather than just symptom management. This therapy has the potential to be an important pillar in improving the overall quality of life of DM patients.

FURTHER STUDY

Further studies are recommended to evaluate the long-term efficacy, safety, and systemic vascular benefits of daily tadalafil use in diabetic patients with erectile dysfunction, particularly within the Indonesian population. Future research should focus on randomized controlled trials with extended follow-up periods to assess its impact on metabolic parameters such as insulin sensitivity and HbA1c levels. Additionally, studies examining cost-effectiveness and integration into Indonesia's healthcare system are essential to ensure accessibility and sustainable implementation. Local data will strengthen clinical guidelines and support personalized treatment strategies for chronic and refractory ED in diabetic patients.

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