Austin Journal of Endocrinology and Diabetes

Open Access

Austin Publishing Group

Mini Review

Treatment of Erectile Dysfunction in Patients with Diabetes

Zahidul Islam Khan[1]* and Faizur Rahman[2]

[1]Department of Biological and Biomedical Sciences, School of Health and Life Sciences, Glasgow Caledonian University, Cowcaddens Road, Glasgow, G4 0BA, UK

[2]Department of Gynaecology and Obstetrics, Zamzam Hospital Ltd. Chakaria, Cox's Bazar, Bangladesh

***Corresponding author:** Zahidul Islam Khan, Department of Biological and Biomedical Sciences, School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK

Received: September 27, 2022; **Accepted:** October 20, 2022; **Published:** October 27, 2022

Abstract

Diabetes and erectile dysfunction often go hand in hand. Different types of medications and therapies are required for the effective management of erectile dysfunction. Treatment options for erectile dysfunction in diabetes patients are discussed in this article. Effectiveness and limitation of the medications have been clarified here and, finally, side effects and contraindication of different medications for erectile dysfunction management have also been reflected. Erectile dysfunction treatment in diabetes patients not only depends on selecting proper medication, but glycaemic control also; therefore, both diabetes and ED are required to treat simultaneously.

Keywords: Erectile Dysfunction; Diabetes; Phosphodiesterase type 5 inhibitors; Testosterone; Prostaglandin E1

Abbreviations

cAMP: Cyclic adenosine monophosphate; **cGMP:** Cyclic guanosine monophosphate; **ED:** Erectile Dysfunction; **MMAS:** Massachusetts Male Aging Study ; **NSAIDS:** Non-steroidal anti-inflammatory drugs; **PDE5**: Phosphodiesterase type 5; **PGE1:** Prostaglandin E1; **PGE0:** Prostaglandin E0; **PCV:** Packed Cell Volume

Introduction

Diabetes mellitus is considered as one of the most common causes of sexual dysfunction both in men and women. Study has shown that diabetic males have three times more chance to develop erectile dysfunction than the non-diabetic males. "Erectile Dysfunction (ED) is defined as the persistent incapability to attain or maintain penile erection for effective sexual intercourse, causing decreased quality of life in males". However, ED is commonly occurring sexual disorder in men and prevalence increases with the age [1]. The Massachusetts Male Aging Study (MMAS) found that the prevalence of ED increased from 40% to 70%with the increment of age from40to 70 years [2].

Factors responsible for the development of ED are diabetes, hypertension, excess alcohol intake, hypogonadism, smoking, some anti-hypertensive (β blockers and diuretics), anti-psychotic drugs (haloperidol, amisulpride and risperidone), and pelvic surgery [3,4,5]. In addition, ED is associated with different aetiologies including neurogenic, vasculogenic, hormonal, drug induced, cavernous impairment, and psychological. The aetiologies are divided into two categories such as psychological and organic. However, mixed aetiologies (both psychogenic and organic) are found almost in all ED patients [6].

Diabetes Induced Erectile Dysfunction (DIED) has multi factorial aetiologies and no single aetiology is at the forefront in the pathophysiology of DIED. In patients with diabetes, the proposed mechanisms of ED includes, increased oxygen free radicals, elevated level of advanced glycation end-products, impaired nitric oxide synthesis, impaired cyclic Guanosine Monophosphate (cGMP) dependent protein kinase-1, increased endothelin B receptor binding sites and up-regulated RhoA/Rho-kinase pathway and neuropathic damage [7].

Erectile dysfunction frequently affects the quality of life of all diabetic patients. Since the patients are normally unwilling to come forward with their problems, proper history taking is one of the most important steps to identify ED in a patient [8]. After finding out the causes of ED, first-line therapy (based on effectiveness and safety) can be started. If first line therapy fails, patients can be referred to a specialist for definite tests and proper care [8].

Management of erectile dysfunction involves both lifestyle changes and treatment of organic or psychological dysfunctions. In addition, creating awareness in a patient and his partner about the effectiveness, safety, adverse effects, and usefulness of a treatment approach is also a vital component of ED management. However, patient's preferences and wishes should be the first priority in the treatment of ED [9].

Since ED in diabetic patients has very complex aetiologies, a broaden approach is required for treating this condition. Correction of modifiable risk factors and lifestyle modification are in the 1st step of this strategy, whereas, using phosphodiesterase type 5 inhibitors are considered as first line therapy in ED management [1].

Phosphodiesterase type 5 inhibitors (PDE5- inhibitors)

PDE5 inhibitors are revolutionary medications for the treatment of sexual dysfunction [10]. They are the first choice medications for treatment of ED because of their effectiveness and safety profile, another fact is that they are non-invasive [11]. Basically they block the PDE5 isoenzyme activity; PDE5 inhibitors prevent the breakdown of cyclic Guanosine Monophosphate (cGMP), thus increase the level of cGMP in the cavernous smooth muscle. Finally, this increased level of cGMP triggers vasodilation and facilitates penile erection [10]. Amusingly, caffeine has some PDE5 inhibitory property. Subjective reports suggested that caffeine improve sexual dysfunction in men [12].

Citation: Khan ZI and Rahman F. Treatment of Erectile Dysfunction in Patients with Diabetes. Austin J Endocrinol Diabetes. 2022; 9(2): 1096.

At present sildenafil, vardenafil and tadalafil are widely available PDE5 inhibitors in market; other PDE5 inhibitors like udenafil and mirodenafil are also available in some countries. Although they have different in characteristics, they are very similar in their effectiveness and safety profile. In addition, some studies have shown that effectiveness of PDE5 inhibitors in diabetic patients is slightly lower than that of non-diabetic counterpart [1].

Structurally both sildenafil and vardenafil are very similar, whereas, tadalafil is little different, due to their structural dissimilarity, pharmacokinetics of these drugs are also different. Plasma half-lives of sildenafil and vardenafil are 4 hours, and for tadalafil are near 18 hours [9]. Moreover, fatty food impairs the absorption of sildenafil and vardenafil, but tadalafil has no possibility of such problem. All these pharmacokinetics make tadalafil different from other PDE5 inhibitors, because of having these advantages tadalafil ensures spontaneity in sex as well as successful intercourse [11].

Proper dosing of PDE5 inhibitors is very important, because inappropriate dose may lead to treatment failure. Sildenafil can be started from 50 mg and increased up to 100mg for achieving maximum benefits. However, more than 100 mg can also be used but there is a chance of higher adverse effects with that. Dose should not be more than 25 mg for old patients, patients with chronic renal disease and liver cirrhosis. Moreover, vardenafil and tadalafil can be started from 10mg and increased to 20 mg for maximum response [13].

Although tolerability of PDE5 inhibitors in sexual dysfunction patients is well, there are some possibilities of adverse reactions with the use of these medications. Most commonly reported adverse effects of this group of drugs are flushing, headache, nasal blockage, nasopharyngitis, indigestion. In addition, prolong and painful erection (priapism) is a rear adverse effect but serious one, because it may leads to permanent penile destruction. Patients should have to contact immediately with his physician, if experienced this condition. Moreover, patients can experience visual impairment, hearing loss, muscle pain and back pain due to using PDE5 inhibitors. Back pain and muscle pain normally disappear within 48 hours without any medications. If pain does not resolve within this time patients can be advised to take NSAIDS for relieving pain [14]. However, study has shown that PDE5 inhibitors mainly tadalafil is not associated with muscle pain in the diabetic patients. One of the commonest adverse effects of sildenafil is visual impairment, which occurs due to relative selectiveness of this drug to the PDE6. Normally isoenzyme PDE6 is found in the retina of eye. On the other hand, vardenafil and tadalafil are less selective to the PDE6 isoenzyme of retina that is why they don't impair visual functions [15].

As mechanism of action of all PDE5 inhibitors are very close to each other, contraindications of these are also similar. Patients suffering from severe cardiovascular disease should be restricted to use of PDE5 inhibitor and other ED treatment as well. In addition, patients getting nitrates therapy should not be given PDE5 inhibitors as there is a chance of developing serious hypotension and life threatening shock. However, for some cases nitrates (long acting) can be withdrawn if patient's coronary condition permits and can be treated with Phosphodiesterase type 5 inhibitors without facing any difficulty. Moreover, patients who are on α blocker therapy can also use PDE5 inhibitors by maintaining some precautions [11].

A range of factors can lead to ED treatment failure including severe underlying pathophysiology, inappropriate pharmacotherapy, unstable relationship between partners, impractical patient's demands, severe anxiety and other emotional problems.

Some alternatives management are also available for the non-responders to phosphodiesterase type 5 inhibitors, for instances intraurethral suppositories (PGE-1), intracavernosal injection therapy (PGE-1), vacuum constriction devices, implantation of penile prosthesis, and vascular surgery [16].

Indeed, it is a concerning matter for those patients who don't like to have alternatives management, after failure of maximum dose of PDE5 inhibitors. On account of these reasons, responsible factors for treatment failure should be inspected carefully. In addition, testosterone level should be measured for detecting hypogonadism. If hypogonadism present, testosterone replacement therapy can be started [16].

Testosterone replacement therapy

It is known that there is a fall of testosterone levels in type 2 diabetes patients. However, this decrement of testosterone levels (less than 8.7 nmol/L) in diabetes patients may be due to obesity and old age [17,18]. On the other hand, some studies suggest that low testosterone level itself a risk factor for diabetes [19]. Testosterone replacement therapy is a desirable option for those patients who have hypogonadism. For the treatment of ED, which is caused by hypogonadism, either testosterone alone or combination of both testosterone and PDE5- inhibitor can be used [9].

Effect of PDE5 inhibitors (sildenafil) greatly depends on the presence of Nitric Oxide (NO). Moreover, NO levels in penis are related to the androgen levels. However, laboratory rats showed significantly diminished the expression of nitric oxide synthase in the presence of testosterone. Furthermore, required serum testosterone concentrations for optimum effects of nitric oxide synthase and PDE5 are undetermined yet. Study showed that patients who failed to get the benefits PDE5 inhibitors therapy due to hypogonadism, after testosterone replacement therapy their conditions were improved [20].

Different types of testosterone preparations are available in market to restore testosterone levels in males such as topical, oral, subcutaneous, transdermal and intramuscular preparations. Among them, most of the patients choose topical gel preparation instead of injection or transdermal patch because of the easiness to use [21].

Adverse effects of testosterone therapy depend on different factors such as age, life situations, and some medical conditions. Testosterone replacement therapy increases the risk of prostate cancer and Benign Prostatic Hyperplasia (BPH). Other reported side effects are hepatic toxicity and neoplasm, polycythemia, gynecomastia, skin problem, sleep apnea, testicular atrophy and infertility. However, for people who want to be a father testosterone therapy is not recommended, as this therapy can suppress hypothalamic-pituitary-thyroid axis [19].

Main contraindication of testosterone therapy is prostatic cancer. This therapy is also contraindicated in some physical conditions such as, palpable prostatic swelling and nodule, lower urinary tract

symptoms, patients with Prostatic Specific Antigen (PSA) more than 4 ng/ml, individual with severe sleep apnea, uncontrolled heart failure, patients with Pact Cell Volume (PCV) more than 50%, and individual with family history of prostate cancer mainly in 1st degree relatives [21].

Intracavernous/intraurethral agents (PGE1)

Prostaglandin E1(PGE1) is the most common medication for the use of intracavernous injections, either alone or in combination with other medication. Intracavernous injection of PGE1 responds nearly in 40- 70% of ED patients. This agent mainly acts by stimulating prostaglandin receptor. PGE1 is converted in PGE0 (active form) within the penis, which increases the level of cAMP. This increased level of cAMP causes penile erection. For treatment of severe vasculogenic ED patients PGE1 can be used [12]. It can be also prescribed when PDE5 inhibitors are contraindicated [22]. Alprostadil is only drug which was approved by FDA in 1994 for intracavernous use [23].

Disadvantages of parenteral injections are painful invasive procedure, need education before applying this, sometimes prolong erection, fibrosis due to multiple injections, and poor patients compliance [22].

Alprostadil for intraurethral use was approved in 1997 for the treatment of ED. Although its efficacy (30-66%) is lower than the parenteral preparation, it acts as a better alternative to parenteral injection. Mechanism of action is similar to the intracavernous injection preparation. However, neither nitric oxide nor intact nerve is required for the action of alprostadil, it can act individually. For treatment of pure neurogenic ED patients, this preparation can be used [23]. Advantages of the intraurethral therapies are non-invasive procedure and easily administrable, whereas, disadvantages are inconstant efficacy and intolerance [22].

If there is any treatment failure, patients are required to educate well about the treatment strategies, and sometimes switching of drugs may resolve the problems. After that, if PDE 5 inhibitors fail again patients can be advised Intracavernous/intraurethral medications. Finally, some non-pharmacological and surgical interventions may be helpful for those patients who are dissatisfied with the pharmacological treatment. If patient is dissatisfied with other treatment modalities or if there is lack of efficacy, penile prostheses can be considered as the best alternative for diabetes induced ED [7].

Many studies have shown that erectile dysfunction is largely associated with poor glycaemic control. In addition, several cross sectional studies demonstrate that better control of blood glucose levels in diabetes patients can improve ED [7].

Conclusion

As erectile dysfunction largely affects the quality of life of the patients, it should be treated well to ensure patient's wellbeing. Diabetes is a complex disease, so treatment of ED in diabetes patients will also be complex. Both ED and diabetes will be treated simultaneously, as success of ED treatment greatly depends on glycaemic control.

Treatment success also depends on several other factors, such as, age of the patients, patients wish, physical condition, proper dosing and many more. During ED treatment these factors should be considered. Moreover, side effects and contraindications of the drugs need to be considered.

Acknowledgement

We would like to thank Dr Jane Nally, Ex- Course leader of MSc Diabetes Care and Management at Glasgow Caledonian University, UK, for her support and inspiration to write this article for completion of an MSc course work.

References

1. Maiorino MI, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. Diabetes Metab Syndr Obes. 2014; 7: 95-105.
2. Hatzimouratidis K. Sildenafil in the treatment of erectile dysfunction: an overview of the clinical evidence. Clin Interv Aging. 2006; 1: 403-414.
3. Mills JN, Barqawi A, Koul S, Koul H, Meacham RB. The Molecular Basis of Erectile Dysfunction: From Bench to Bedside. Rev Urol. 2005; 7: 128-134.
4. Doumas M, Douma S. The effect of antihypertensive drugs on erectile function: a proposed management algorithm. J Clin Hypertens (Greenwich). 2006; 8: 359-364.
5. Park YW, Kim Y, Lee JH. Antipsychotic-induced sexual dysfunction and its management. World J Mens Health. 2012; 30: 153-159.
6. Coward RM, Casson CC. Tadalafil in the treatment of erectile dysfunction. Ther Clin Risk Manag. 2008; 4: 1315-1330.
7. Thorve VS, Kshirsagar AD, Vyawahare NS, Joshi VS, Ingale KG, et al. Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management. J Diabetes Complications. 25: 129-136.
8. Basu A, Ryder RE. New treatment options for erectile dysfunction in patients with diabetes mellitus. Drugs. 2004; 64: 2667-88.
9. Bella AJ, Lee JC, Carrier S, Benard F, Brock GB. 2015 CUA Practice guidelines for erectile dysfunction. Can Urol Assoc J. 2015; 9: 23-29.
10. Viigimaa M, Vlachopoulos C, Lazaridis A, Doumas M. Management of erectile dysfunction in hypertension: Tips and tricks. World J Cardiol. 2014; 6: 908-915.
11. Raheem AA, Kell P. Patient preference and satisfaction in erectile dysfunction therapy: a comparison of the three phosphodiesterase-5 inhibitors sildenafil, vardenafil and tadalafil. Patient Prefer Adherence. 2009; 3: 99-104.
12. Steers WD. Pharmacologic Treatment of Erectile Dysfunction. Rev Urol. 2002; 4: S17-25.
13. McMahon CN, Smith CJ, Shabsigh R. Treating erectile dysfunction when PDE5 inhibitors fail. BMJ. 2006; 332: 589-592.
14. Huang SA, Lie JD. Phosphodiesterase-5 (PDE5) Inhibitors In the Management of Erectile Dysfunction. Pharmacy and Therapeutics. 2013; 38: 414-419.
15. Vickers MA, Satyanarayana R. Phosphodiesterase type 5 inhibitors for the treatment of erectile dysfunction in patients with diabetes mellitus. Int J Impot Res. 2002; 14: 466-471.
16. Park NC, Kim TN, Park HJ. Treatment Strategy for Non-Responders to PDE5 Inhibitors. The World J Mens Health. 2013; 31: 31-35.
17. Betancourt-Albrecht M, Cunningham GR. Hypogonadism and diabetes. Int J Impot Res. 2003; 4: S14-20.
18. Haring R, Völzke H, Steveling A, Krebs A, Felix SB, et al. Low serum testosterone levels are associated with increased risk of mortality in a population-based cohort of men aged 20-79. Eur Heart J. 2010; 31: 1494-501.
19. Bassil N, Alkaade S, Morley JE. The benefits and risks of testosterone replacement therapy: a review. Ther Clin Risk Manag. 2009; 5: 427-448.
20. Mulhall JP. Treatment of Erectile Dysfunction in a Hypogonadal Male. Rev Urol. 2004; 6: S38-40

21. Ullah MI, Riche DM, Koch CA. Transdermal testosterone replacement therapy in men. Drug Des Devel Ther. 2014; 8: 101-112.

22. Young B. Sexual dysfunction in Diabetes' MMC122347-15-A, Glasgow Caledonian University, Room CEE6. 2015.

23. Nehra A. Oral and Non-Oral Combination Therapy for Erectile Dysfunction. Rev Urol. 2007; 9: 99-105.