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ORIGINAL RESEARCH

Metformin's Effect on Erectile Dysfunction: A Comprehensive Review

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ABSTRACT

Erectile dysfunction (ED) is a medical condition characterized by the inability to get or maintain an erection firm enough for sexual intercourse.Metformin belongs to a class of drugs known as biguanide and is an insulin sensitizer. It decreases insulin resistance by glucose uptake and use by target tissues, thereby decreasing insulin resistance.Metformin exerts various beneficial effects beyond glucose lowering, including immune modulation, anti-atherosclerosis, anti-cancer, anti-aging, anti-microbial, and anti-inflammation, and also reduces erectile dysfunction.ED mechanisms can include endothelium-dependent vasodilatory, sympathetic nerve activity elevation, and atherosclerotic luminal narrowing.

Additionally, these insults have been linked to an insulin-resistant state, which in turn is comorbid with obesity, dyslipidemia, diabetes, and hypertension.

This study is dedicated to exploring the potential of metformin in the treatment of ED, with a focuson the mechanisms involved.

After a thorough review of numerous studies, it can be confidently stated that metformin could be a valuable adjunct in the treatment of ED in men with metabolic syndrome or diabetes who are in need of oral hypoglycemic therapy.

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INTRODUCTION

Erectile dysfunction (ED) is a medical condition characterized by the inability to get or maintain an erection firm enough for sexual intercourse.An epidemiological study of sexual disorders in south Indian rural population suggested that prevalence of erectile dysfunction was found to be 15.77%, male hypoactive sexual desire disorder (HSDD) 2.56%; premature ejaculation was found to be prevalent in 8.76% of the male subjects(1).Erectile dysfunction (ED) can indeed be linked to weight gain and obesity. Excess weight, especially when it leads to conditions like diabetes, hypertension, or cardiovascular disease, can contribute to ED.

Metformin is a drug commonly prescribed for the treatment of type 2 diabetes mellitus. It belongs to a class of medications called biguanides and works by decreasing the amount of glucose produced by the liver and increasing the body's response to insulin. Metformin exerts various beneficial effects beyond glucose lowering, including immune modulation, anti-atherosclerosis, anti-cancer, anti-aging, anti-microbial, and anti-inflammation.Metformin, an insulin sensitizer and multimodal metabolism modulator, affects vascular physiology and, subsequently, erectile function.

Mechanisms of ED have been:

1. endothelium-dependent vasodilatory impairmentmediated by reduced bioavailability of nitric oxide (NO);
2. sympathetic nerve activity elevationresulting in enhanced basal and myogenic tone within the corpus cavernosum;
3. atherosclerotic luminal narrowing, yielding reduced penile arterial inflow (2).

Furthermore, these insults have been linked to an insulin-resistant state, which in turn is comorbid with obesity, dyslipidemia, diabetes, and hypertension.

Metformin's role in addressing these conditions provides a sense of reassurance in the management of ED.

Insulin resistance is a significant risk factor for ED(3).

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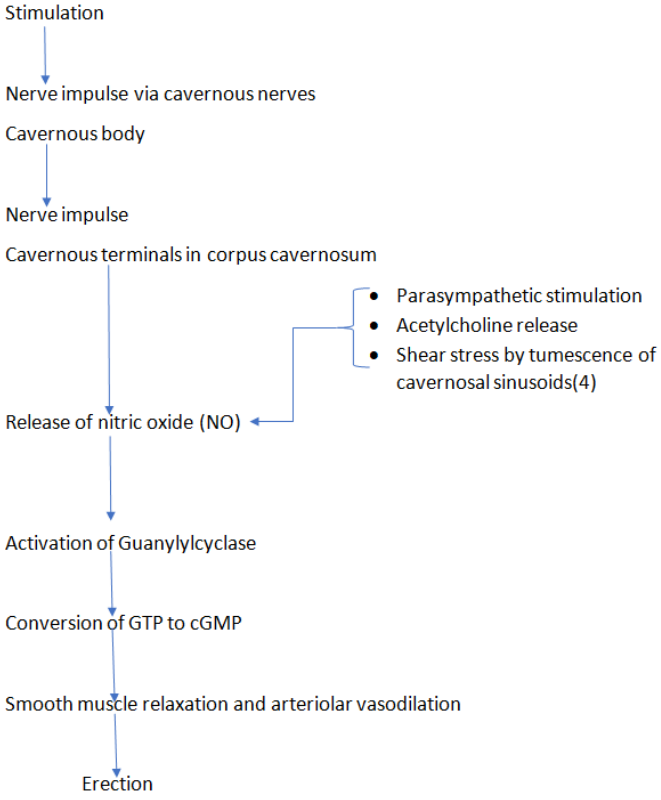
Mechanism of endothelium-dependent vasodilation by NO



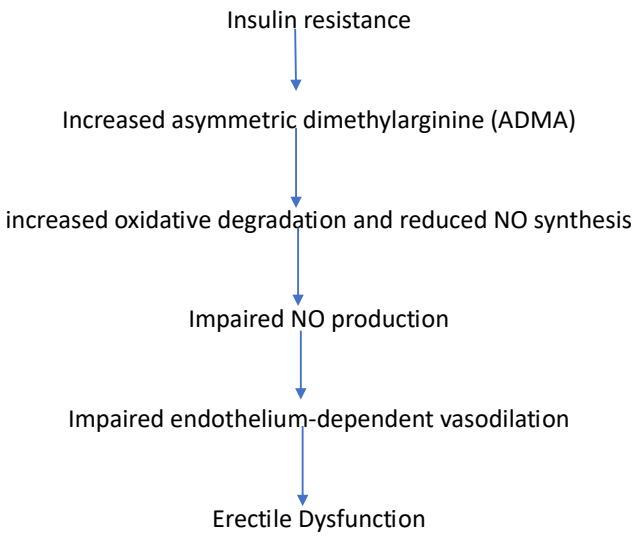
- Impairment in NO productioncan impair endothelium-dependent vasodilation, leading to ED.
- Insulin resistance induces a state of NO deficiency, which is attributed to increased oxidative degradation and reduced NO synthesis. Metformin is an insulin sensitizer and thus might help normalize NO levels.

Insulin resistance as a risk factor for ED

Insulin resistance has been found to be a major risk factor for ED. In case of insulin resistance, basal levels of serum insulin are elevated which contribute to ED by following:

1. Reducing the bioavailability of NO and inducing vasoconstriction;
2. Increasing activity of the sympathetic nervous system;
3. Promoting other risk factors such as hypertension.

Insulin resistance induces NO deficiency through following mechanism:



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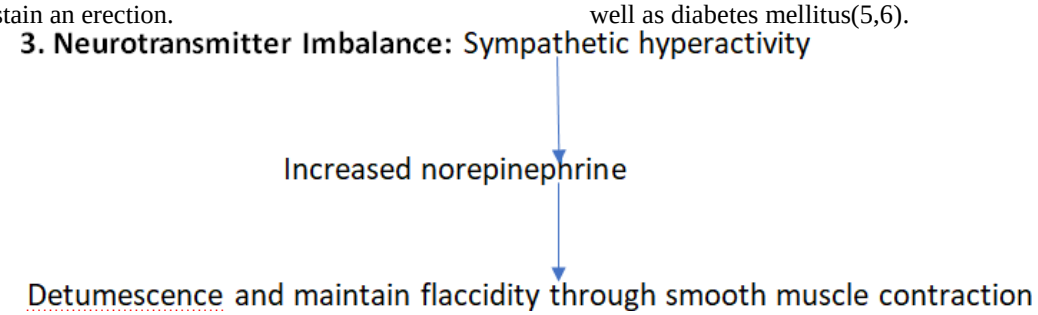
Mechanism of sympathetic hyperactivity in ED

Sympathetic hyperactivity can contribute to ED:

1. **Vascular Effects:** Sympathetic hyperactivity can lead to vasoconstriction (narrowing of blood vessels) throughout the body, including those in the penis. This constriction can reduce blood flow to the penis, making it difficult to achieve and sustain an erection.
2. **Psychological Factors:** Chronic sympathetic hyperactivity is often associated with increased stress, anxiety, and emotional tension. These psychological factors can contribute to ED by affecting arousal and sexual performance.Sympathetic hyperactivity has been known to occur both in essential hypertension as well as diabetes mellitus(5,6).



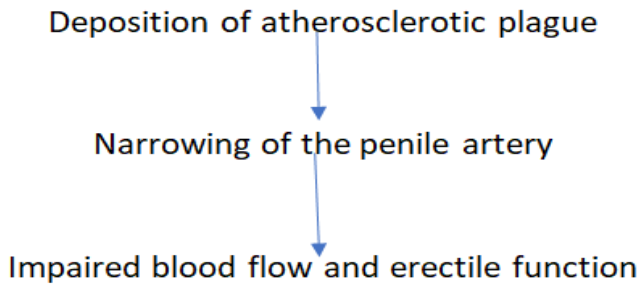
Elevated levels of norepinephrine, a well-established marker for sympathetic hyperactivity, have been demonstrated in human studies of both essential hypertension and obesity (7).

4. **Hormonal Influence:** Sympathetic hyperactivity can also affect hormone levels, including cortisol (a stress hormone), which may further contribute to ED by disrupting normal endocrine function.

- Metformin's sympathetic neuromodulatory effects, including heart rate and blood pressure modulation, can help against ED.

Mechanism of atherosclerotic luminal narrowing

Atherosclerosis is a condition where fatty deposits called plaques build up inside the arteries (8). These plaques are made up of cholesterol, fatty substances, cellular waste products, calcium, and fibrin (a clotting material in the blood). Over time, these plaques can harden and narrow the arteries, reducing blood flow to vital organs and tissues.



- Metformin helps lower cholesterol and blood pressure to some extent, thereby reducing the formation of atherosclerotic plaque.

Brief of metformin

Metformin, as the only biguanide and an insulin sensitizer, plays a crucial role in preventing ED. It achieves this by reducing insulin resistance, preventing the degradation of NO, and to someextent, preventing ED. Importantly, metformin does not promote insulin secretion, thereby reducing the risk ofhypoglycemia.

Mechanism of action

- The mechanism of metformin is a reduction in hepatic gluconeogenesis(9).
- Metformin may also slow intestinal absorption of sugars (9).
- It improvesperipheral glucose uptake and utilization (9).

Weight loss may occur because metformincauses loss of appetite.

Pharmacokinetics: Metformin is well absorbed orally; it is not bound toserum proteins and is not metabolized. Excretion occurs via the urine (9).

Adverse effects: It may cause diarrhea, nausea, and vomiting. In some cases, it may lead to lactic acidosis. It is contraindicatedacute myocardial infarction, sepsis, exacerbation of heart failure, ordisorders that may lead to acuterenal failure. Long-term use may be associated with vitamin B12deficiency (9).

Studies for endothelium-dependent vasodilatation

Animal studies:

(1) The following study designproposed by Kim et al.,

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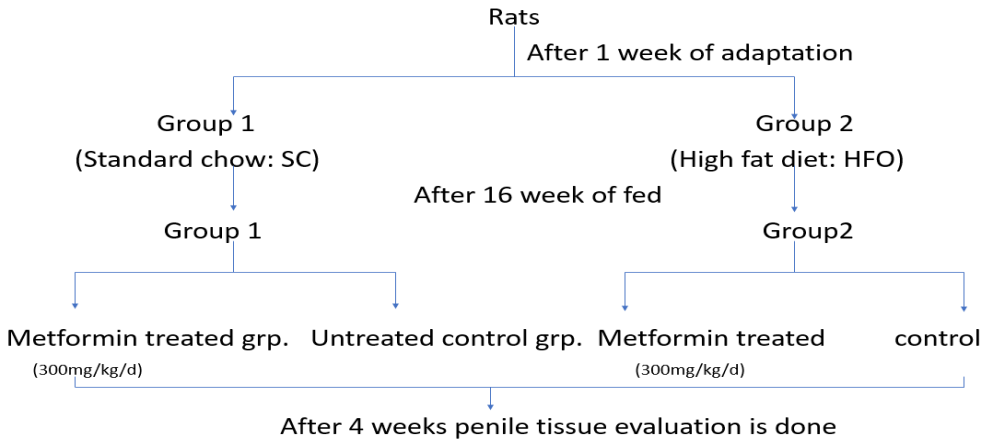
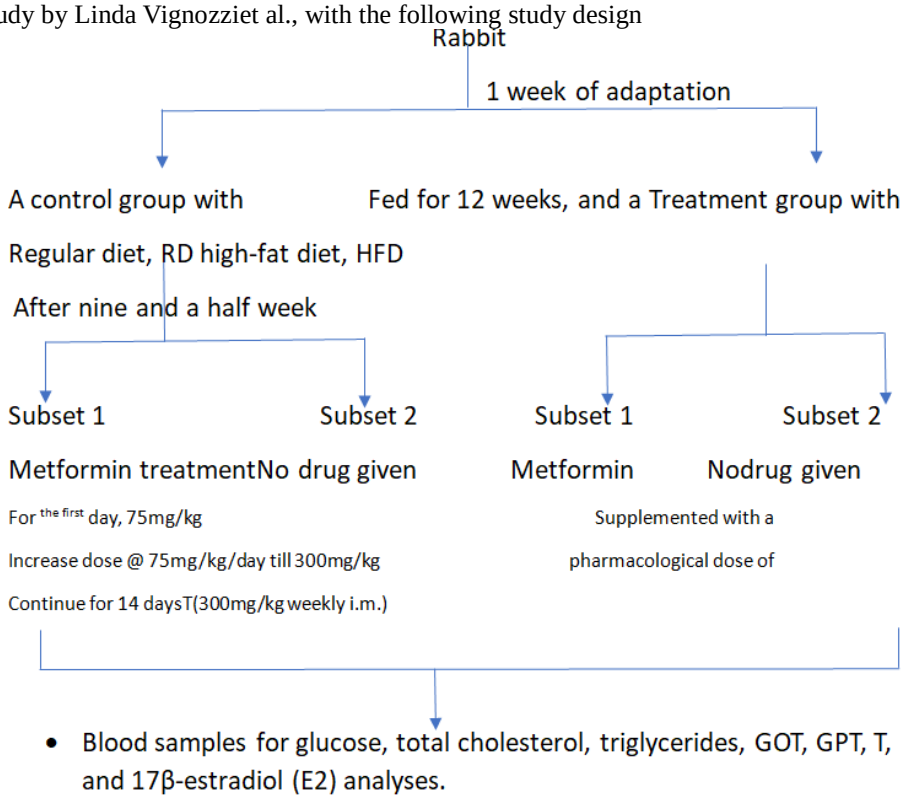


This study showed that treatment with metformin restores transcription of endothelial NO synthase in the penile tissue of obese rats as well as resolved insulin resistance (10).

(2) Another study by Linda Vignozziet al., with the following study design



- Blood samples for glucose, total cholesterol, triglycerides, GOT, GPT, T, and 17β-estradiol (E2) analyses.
- After sacrifice seminal vesicles, prostate, and visceral fat were harvested from the different experimental groups and appropriately stored for subsequent analyses.

This study concluded that metformin treatment increased NO synthase levels, which subsequently increases NO levels, leading to better vasodilation and erection (11).

Clinical studies:

(3) Randomized, parallel, placebo-controlled study conducted by Vitale et al. on Sixty-five subjects with metabolic syndrome who were allocated to receive metformin 500 mg twice daily (n = 32) or placebo (n = 33) for 3 months, showed metformin improved endothelium-dependent vasodilation compared with those treated with placebo (12).

(4) In a study conducted by E Diamanti-Kandarakiset al.,over 40 females (20 PCOS subjectsand 20 control) in which metformin (1700 mg daily) was administered for 6 months to the PCOS group, it was found thatflow-mediated dilatation (FMD) on the brachial arterysignificantly improved after metformin treatment, i.e., improvement in endothelial function (13).

(5) It was observed that metformin use causesbasal vessel diameter, and the FMD increased, thus showing an improved endothelial function in a

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study conducted byD Romualdiet al. However, it was observed that reduced testosteroneand 17-hydroxyprogesterone levels without affecting glucose-insulinemic parameters(14).

(6) Luiz Guilherme Kraemer de Aguiaret al. conducted a double-blind study (where 16 subjects received metformin and 15 were on placebo) in 31 subjects who were first-degree relatives of type 2 diabetic patients and who had metabolic syndrome and normal glucose tolerance. It was observed that metformin improved vascular endothelial reactivity in first-degree relatives with metabolic syndrome in type 2 diabetic patients (15).

(7) In a study byK J Matheret al. on 44 diabetic subjects out which 29 received metformin 500mg twice daily and 15 were on placebo for 12 weeks, before and after treatment, blood flow responses to intraarterial administration of endothelium-dependent (acetylcholine), endothelium-independent (sodium nitroprusside) and nitrate-independent (verapamil) vasodilators were measured using forearm plethysmography. It was observed that subjects who received metformin demonstrated statistically significant improvement in acetylcholine-stimulated flows compared with those treated with placebo, whereas no significant effect was seen on nitroprusside-stimulated or verapamil-stimulatedflows. There was a significant improvement in insulin resistance with metformin (16).

Studies for sympathetic hyperactivity

(1) Soffia Gudbjornsdottiret al.conducted a placebo-controlled, double-blind, crossover-design study on Six mildly hypertensive and moderately obese men who had been treated for hypertension for at least 1 year.Three weeks after discontinuing the antihypertensive medication, each patient was allocated randomly to metformin 850 mg b.i.d. or placebo. It was observed that resting right renal NEspillover (RR NE sp) and total body NE spillover (TB NE sp), as well as resting muscle sympathetic nerve activity, remained unchanged with metformin treatment(17).

(2) A double-blind, randomized crossover study by P Sundaresanet al.on fourteen diabeticpatients receiving metformin or glibenclamidewere tested for forearm vascular responsiveness to intrabrachial arterial infusion of diazoxide (an ATP-sensitive potassium channel opener), acetylcholine, sodium nitroprusside, and norepinephrine, BP responses to intravenous infusions of NE and angiotensin II, BP responses to cold pressor testing and isometric exercise, and 24-h ambulatory BP monitoring.It was observed that plasma norepinephrine levels were significantly higher on glibenclamide, and systolic BP responses to intravenous norepinephrine and angiotensin II were significantly higher on glibenclamide than on metformin however, both drugs produced similar glycaemic effects, and mean 24-h BPs did not differ between the two groups, but mean 24-h heart rates were significantly loweron glibenclamide therapy than on metformin (18).

(3) Daniela Manzellaet al.tried to evaluate the effects of metformin onarterial blood pressure (BP) and the cardiac sympathetic nervous system. They considered thathyperinsulinemia/insulin resistance and elevated plasma free fatty acids levels are involved in hypertension and cardiac sympathetic overactivity. Metformin improves insulin action and lowers plasma-free fatty acid concentrations. For this study they enrolled 120 overweight type 2 diabetic patients were treated with placebo (n = 60) + diet or metformin (850 mg twice daily) (n = 60) + diet for 4 months. Subjects who were on metformin showed a decrease in fasting plasma glucose, insulin, triglyceride, and free fatty acid concentrations and HOMA index.Metformin treatment was also associated with a significant improvement in cardiac sympathovagal balance but not in mean arterial BP (19).

Studies foratherosclerotic luminal narrowing

(1) A study conducted inDiabetes Prevention Program Coordinating Center, Biostatistics Center, GeorgeWashington University, Rockville, Maryland, on 3,234 individuals with impaired glucose tolerance randomly assigned to receive intensive lifestyle intervention, metformin, or placebo. Assessment of blood pressure, lipids, electrocardiogram, and CVD events was undertaken, and it was found that triglyceride levels fell in all treatment groups but fell significantly more with intensive lifestyle intervention. Total cholesterol and LDL cholesterol levels were similar among treatment groups. Intensive lifestyle intervention significantly increased the HDL cholesterol level and reduced the cumulative incidence of the proatherogenic LDL phenotype B. This study concluded that lifestyle intervention improves CVD risk factor status compared with placebo and metformin therapy(20).

(2) Die Huet al.conducted an open-label, placebo-controlled, randomized trialon nondiabetic patients with coronary artery disease. They randomized patients into CLA (Cholesterol-Lowering Agents alone: atorvastatin+/-ezetimibe, n=38) and Met+CLA groups (metformin plus CLA, n=33) at a 1:1 ratio. After one month, metformin significantly reduced LDL-C (-20.81%, P<0.001), enabling 72% of patients to attain guideline-recommended LDL-C goals. Noteworthy reductions in PCSK9 levels (-15.03%, P<0.001) were observed(21).

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(3) Genome-wide association studies (GWAS) were performed by Mengling Qiet al.for 168 ECG trace characteristics (ETCs) extracted from the 12-lead ECGs of 42,340 Europeans in the UK Biobank. Regression model and linkage disequilibrium score regression (LDSC) identified significant phenotypic and genetic correlations of T-wave area in lead aVR (aVRT-area) with the usage of diabetes medications (ATC code: A10 drugs and metformin) and the risks of ischemic heart disease (IHD) and coronary atherosclerosis (CA). It was found that Patients taking diabetes medications are prone to have decreased aVRT-area and an increased risk of IHD and CA (22).

(4) Ali Akbar Soleimaniet al.cultured human vascular smooth muscle cells in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 (DMEM-F12) medium and were treated with different values of Metformin and Dexamethasone.The BARR2 gene and protein expression levels were identified with RT-qPCR and western blotting techniques, respectively.The results of this study showed that metformin and dexamethasone suppress the BARR2 protein and gene expression levels. Since BARR2 is known to be involved in cell growth,thus the study suggested that Metformin and Dexamethasone might inhibit vascular smooth muscle cellproliferation and migration (23).

Studies showing metformin's effect on ED

Animal studies:

(1) Hicham Labaziet al.conducted an experiment on Male Sprague-Dawley rats, where these rats were implanted with mini-osmotic pumps containing saline or Angiotensin II (70 ng/min, 28 days). Animals were then treated with metformin or vehicle during the last week of Angiotensin II infusion.It was found that metformin treatment improved erectile function in the Angiotensin II-treated rats.Metformin treatment also resulted in an increase in eNOS phosphorylation at ser1177 (24).

(2) Fábio H Silvaet al. conducted a study on C57BL/6 male mice where these were fed for 10 weeks with a standard chow or high-fat diet and were treated with metformin (300 mg/kg/day, 2 weeks). Intracavernosal pressure (ICP) and in vitro, corpus cavernosum (CC) relaxations to both acetylcholine and electrical field stimulation, as well as phenylephrine-induced contractions, were recorded. It was found that treatment with metformin restored erectile function in obese mice through improvement of in vitro endothelial and nitrergic cavernosal relaxations (25).

Clinical study: Gastón J Rey-Valzacchiet al.conducted a prospective, randomized, controlled, double-blind placebo study on 30 male patients with erectile dysfunction, insulin resistance, and poor response to sildenafil. After randomization, 17 patients were given metformin, and 13 patients were on placebo. Erectile function was rated according to the International Index of Erectile Function 5 (IIEF-5); insulin resistance was measured by homeostasis model assessment (HOMA; IR = HOMA ≥ 3).After treatment with metformin, patients with ED showed a significant increase in IIEF-5 score and a significant decrease in HOMA, while there were no changes in these parameters in patients with ED receiving a placebo (26).

Study showing Erectile dysfunction caused by use of metformin

(1) Min Huang Nguet al.published a case report in which a recently diagnosed 57-year-old diabetic patient suffered erectile dysfunctionfollowing treatment with metformin 500 mg BD. The patient had a known case of hypertension and hyperlipidemiafor the last 2 years and was takingtelmisartan 80 mg OD and atorvastatin 40 mg OD.In the first week of metformin treatment, the patient experienced mild nausea, which completely subsided thereafter.In the second week, he had difficulty achieving an erection despite having sufficient arousal. Screening for anxiety and depression was done, which was not significant in that case. After considering the possibility that this might be a case of metformin-induced erectile dysfunction, treatment with metformin was discontinued and was changed to gliclazide MR 120 mg OD, and then vildagliptin 50 mg BD was added to the regimen.Three days after stopping metformin, his sexual function began to improve, and 2 weeks later, his sexual function returned to normal.To determine whether metformin causes erectile dysfunction, after obtaining informed consent from the patient, metformin 500 mg BD was started again. Within 10 days of taking metformin, he once again experienced difficulty achieving an erection. On day 15, he was rendered completely impotent.Thereafter, metformin was withdrawn.Three weeks after he stopped taking metformin, his sexual function returned to normal, suggesting that erectile dysfunction can be an adverse drug reaction to metformin (27).

(2) Lin Feng et al. conducted a two-sample Mendelian randomization (TSMR) study to examine the causal effect of antidiabetic drugs (including metformin, insulin, and gliclazide) on erectile dysfunction.There was a significant causal relationship between metformin use and ED [Beta: 4.9386; OR:1.396E+02 (95% CI:9.13-2135); p-value: 0.0004), suggesting that metformin increased the risk of ED development. Also, gliclazide increased the risk of ED [Beta: 11.7187; OR:0.0125 (95% CI:12.44-1.21E+09); P

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value: 0.0125). There was no significant causal relationship between insulin use and ED [Beta: 3.0730; OR:21.6071 (95% CI:0.24-1942.38); p-value: 0.1806) (28).

(3) Gorika Tomar et al. conducted a prospective observational investigation study in two groups comprising 30 males taking metformin as a hyperglycaemic agent with T2DM and 30 males without any diabetic treatment to assess the impact of metformin treatment on testosterone levels in male patients with T2DM.This study showed a reduction in testosterone levels, which may lead to low sex drives and induction of low testosterone-induced erectile dysfunction. (29)

CONCLUSION

Erectile dysfunction is a condition faced by many males around the world. There are many predisposing factors to ED, like obesity, hypertension, diabetes, depression, anxiety, stress, etc.ED is believed to be caused by the following mechanisms: (I) endothelium-dependent vasodilatory impairment, (II) sympathetic nerve activity elevation, and (III) atherosclerotic luminal narrowing. In this review, we tried to explain the abovementioned mechanism.

Drug metformin, which is commonly prescribed in the treatment of diabetes, has shown other effects on the body, likeimmune modulation, anti-atherosclerosis, anti-cancer, anti-aging, anti-microbial, and anti-inflammation.In this review, we tried to find the effects of metformin on erectile function. Our observation suggested that metformin reduces insulin resistance cholesterol levels, thereby improving NO levels(which is essential for endothelium-dependent vasodilation)& reducing atherosclerotic-plague formation, respectively, as metformin's sympathetic neuromodulatory effectson heart rate and blood pressure modulation can help against ED.

It is also being observed that metformin can cause erectile dysfunction as an adverse drug reaction, but this is quite rare.

In our opinion, metformin may be considered an adjunct for the treatment of ED in men with metabolic syndrome or diabetes who require oral hypoglycemic therapy.

Acknowledgment

None.

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