Supplementary

Table S1 Characteristics of the included studies

Study (years)	Country	Study design	Diagnosis of the patients	Total number of patients	Inclusion criteria	Exclusion criteria	Age Mean±SD	IIEF score	Other ED evaluations	Assessment intervals
Al Demour *et al.* (2021) (32)	Jordan	Prospective phase 1/2, open-label, single-arm trial	Type 1 or type 2 diabetes	n=22	- Adult male patients - Between the ages of 25 and 75 years - Type 1 or type 2 diabetes with an hemoglobin A1C (HbA1c) level of ≤ 10 - A history of diabetes for at least 5 years - The body mass index (BMI) between 20 and 30 - Baseline International Index of EF (IIEF-5) score of <22 - A history of chronic erectile dysfunction (ED) lasting for at least 6 months - Unresponsiveness to previous medical treatments, such as phosphodiesterase type 5 (PDE5) inhibitors and prostaglandin E1	- Clinically evident penile anatomical deformities (e.g., Peyronie's disease) - History of priapism, skin irritation, infections, or wounds near the injection site - Bleeding or clotting disorders - Use of anticoagulant therapy - Current urinary tract infection - Current or previous infection with human immunodeficiency virus (HIV) or hepatitis viruses - Any previous penile implant - Penile vascular surgery or radical prostatectomy (RP) - Current or previous malignancy - Prostate-specific antigen (PSA) levels >4 ng/mL - Untreated hypogonadism or low serum total testosterone (<200 ng/dL) - Uncontrolled hypertension or hypotension (systolic BP >170 or <90 mm Hg, diastolic BP >100 or <50 mm Hg) - Reported unstable cardiovascular disease (e.g., unstable angina, myocardial infarction within the past 6 months, life-threatening arrhythmia, cardiac failure) - Symptomatic postural hypotension within 6 months prior to screening - Systemic autoimmune disorder - Significant active systemic or localized infection - Use of immunosuppressive medication	59.18±8.45	11.5±2.7	Erection Hardness Score (EHS) Peak systolic velocity (PSV) End-diastolic velocity (EDV) Resistive index (RI)	Baseline 1 month 3 months 6 months 12 months
Al Demour *et al.* (2024) (23)	Jordan	An open-label, single-center, phase 2 pilot clinical trial	Type 1 or type 2 diabetes	n=8	- Between the ages of 25 and 75 years - Type 1 or type 2 diabetes with an hemoglobin A1C (HbA1c) level of ≤ 10 - A history of diabetes for at least 5 years - The body mass index (BMI) between 20 and 30 - Baseline International Index of EF (IIEF-5) score of <22 - A history of chronic erectile dysfunction (ED) lasting for at least 6 months	- Penile anatomical deformities (e.g., Peyronie's disease) - Penile skin irritation, infection, or wound near injection sites - Bleeding or clotting disorders - Current urinary tract infection, or current/previous infection with human immunodeficiency virus (HIV) or hepatitis viruses - Previous penile implant, penile vascular surgery, or radical prostatectomy (RP) - Current or previous malignancy - Prostate-Specific Antigen (PSA) level >4 ng/mL - Untreated hypogonadism or low serum total testosterone (<200 ng/dL) - Uncontrolled hypertension or hypotension (systolic BP >170 or <90 mm Hg, diastolic BP >100 or <50 mm Hg) - Cardiovascular disease (e.g., unstable angina, myocardial infarction within the past 6 months, cardiac failure, life-threatening arrhythmia, congestive heart failure) or symptomatic postural hypotension within 6 months before screening - Systemic autoimmune disorder	55±6.8	10.4±2.8	Erection Hardness Score (EHS) Peak systolic velocity (PSV) End-diastolic velocity (EDV) Resistive index (RI)	Baseline 1 month 3 months 6 months 12 months 24 months
Alhefnawy *et al.* (2023) (33)	Egypt	A pilot trial	Type 2 diabetes	n=10	- Diabetic adult men with hemoglobin A1C (HbA1c) levels between 6.5% and 10% - Diagnosis of diabetes mellitus for more than 5 years - Have a consistent sexually active partner - Inadequate sexual activity despite taking the maximal dosage of oral phosphodiesterase type 5 inhibitors (PDE5Is) during the last eight weeks	- History of bone marrow disorders or neurogenic erectile dysfunction (ED) - Gentamicin hypersensitivity - History of severe cardiovascular disease (e.g., angina, arrhythmias, cardiac failure, stroke) - Renal failure or respiratory failure considered life-threatening - Positive tests for HIV, HBV, HCV, or syphilis - Cancer history within the last five years - Hemoglobin A1C (HbA1c) levels greater than 10% - Uncontrolled hypertension or hypotension (systolic blood pressure > 170 or < 90 mm Hg; diastolic blood pressure > 100 or < 50 mm Hg) - Anticoagulant therapy - Severe infectious disease - Testosterone concentration less than 200 ng/dL - Presence of a penile implant or willingness to receive one. - Alterations in penile morphology - Participation in additional clinical studies within the previous 30 days - Inability to comply with the procedure	52.3±6.4	12.7±2.16	Peak systolic velocity (PSV) End-diastolic velocity (EDV)	Baseline 6 months
Koga and Horiguchi (2021) (34)	Japan	An open-label pilot trial	Organic ED	n=38	-Presented to the hospital for erectile dysfunction (ED) treatment	- Receiving other medications, such as phosphodiesterase type 5 inhibitors (PDE5Is) for erectile dysfunction (ED) or testosterone replacement therapy for late-onset hypogonadism	55.97±13.24	13.05±4.77	-	Baseline 2 weeks 4 weeks 6 weeks
Levy *et al.* (2015) (39)	Florida	A prospective trial	Peyronie disease	n=5	- Aged 18 years or older - Had an acquired penile curvature - Associated with a palpable penile plaque noted during physical examination - Confirmed by ultrasonography screening	- Current warfarin treatment - Inability to achieve adequate erections with penile injection for assessment of penile curvature - History of definitive treatment for prostate, bladder, or other pelvic cancers (e.g., surgery, external-beam radiation therapy, brachytherapy, cryotherapy) - Any history of prostate cancer - Hematologic disorders - Chronic liver disease (e.g., cirrhosis, hepatitis C) - Immune system disorders (e.g., HIV infection) - Psychiatric disorders (e.g., major depression, schizophrenia, bipolar disorder) - Cerebrovascular accident or deep venous thrombosis within the past 5 years - Severe sleep apnea - Clinically significant abnormal laboratory results that, in the investigator's opinion, would increase participant risk or compromise study data integrity - Receipt of investigational drugs within the past 30 days	51.20±5.805	47.60±19.591	Peak systolic velocity (PSV) End-diastolic velocity (EDV) Stretched Penile Length Penile Girth (After Trimix Injection) Penile Curvature/Angle	Baseline 6 weeks 3 months 6 months
Levy *et al.* (2016) (35)	Florida	A prospective, open-label, nonrandomized, single-center trial	Chronic organic ED	n=5	– Men aged 40 to 70 years – Chronic, organic erectile dysfunction (ED) for at least 6 months – Baseline International Index of Erectile Function (IIEF) score of 21 or greater – Involved in a monogamous, heterosexual relationship for at least 3 months, with both partners motivated to have or attempt sexual intercourse at least 4 times per month, beginning 2 weeks after the study treatment – Willing to limit alcohol intake and eliminate the use of recreational drugs for sexual encounters – Willing to undergo an injection – Mentally competent and able to understand all study requirements – Available for all baseline, treatment, and follow-up examinations required by the protocol – Willing to forego participation in any other study during the duration of the present study	-Clinically evident penile anatomical deformities (e.g., Peyronie disease) or a history of priapism -Participation in any non-study intervention for erectile dysfunction (ED) within 4 weeks of study treatment -Uncontrolled hypertension or hypotension (systolic blood pressure >170 mm Hg or <90 mm Hg; diastolic blood pressure >100 mm Hg or <50 mm Hg) -Untreated hypogonadism or low serum total testosterone (<200 ng/dL). -Body mass index (BMI) of 30 or greater -Major medical conditions. -Prostate cancer -Previous pelvic or abdominal radiation therapy -Previous, concomitant, or scheduled use of antiandrogen therapy -Skin irritation, infection, wound, sore, or disruption in the areas of skin entry for penile injection -Previous penile implant or penile vascular surgery -Current or previous malignancy other than localized prostate cancer -Unstable cardiovascular disease (e.g., unstable angina, myocardial infarction within the past 6 months, cardiac failure, life-threatening arrhythmia, congestive heart failure) -Symptomatic postural hypotension within 6 months before screening -Current urinary tract or bladder infection -Systemic autoimmune disorder -Substantial active systemic or localized infection -Use of immunosuppressant medications -Drug, alcohol, or substance abuse within the past 3 years	-	34.62±10.58	Peak systolic velocity (PSV) End-diastolic velocity (EDV) Stretched Penile Width Penile Width After Trimix	Baseline 6 weeks 3 months 6 months
Mirzaei *et al.* (2021) (24)	Iran	A randomized single-blinded clinical trial	Type 2 diabetes	Intervention =10 Control =10	- Aged 50-70 years with erectile dysfunction (ED)	- Those with laboratory or clinical signs of other disorders (especially those associated with erectile dysfunction)	Intervention= 63.8± 7.4 Control= 65.6± 5.1	Intervention=7.2± 2.1 Control=7.2± 2.1	Peak systolic velocity (PSV) End-diastolic velocity (EDV) Resistive index (RI)	Baseline 3 months 6 months
Nguyen *et al.* (2021) (40)	Vietnam	An open clinical phase I/IIa trial without a control group.	A medical disease of reduced sexual activity	n=15	- Males aged 35 to 70 years - reduced sexual desire and testosterone levels of ≤ 12 nMol/dL	- Positive laboratory tests for HBV, HCV, HIV - Coagulation disorders - Cancers - Active infections - Heart failure, kidney failure, or respiratory failure	48.4±7.5	9.08±5.60	-	Baseline 3 months 6 months 12 months
Protogerou *et al.* (2020) (36)	Greece	A prospective phase 1, single center pilot trial	Organic ED	n=5	- Organic erectile dysfunction (ED) due to diabetes mellitus, hypertension, hypercholesterolemia, and Peyronie disease	- Lack of sexual interest - Neurologic or hormonal erectile dysfunction (ED) - Penile injuries other than Peyronie's disease - All cases of cancer	56.80±6.72	10.40±4.56	Peak systolic velocity (PSV) End-diastolic velocity (EDV)	Baseline 1 months 3 months
Yiou *et al.* (2015) (37)	France	A nonrandomized, phase 1/2 pilot clinical trial	Post radical prostatectomy erectile dysfunction (pRP-ED)	n=12	- Men aged 45–70 years who had undergone radical prostatectomy (RP) 6 months to 3 years prior to treat localized prostate adenocarcinoma - Documented post-radical prostatectomy erectile dysfunction (pRP-ED) with penile arterial insufficiency and/or veno-occlusive dysfunction, confirmed using color duplex Doppler ultrasound (CDDU) - Failure of pharmacotherapy defined as an Erection Hardness Score (EHS) <3 after at least 10 intracavernous alprostadil injections (20 mg) combined with sildenafil (100 mg) and the use of a vacuum device	- Not reported	63.6+ 4.2	5.09±1.79	Erection Hardness Score (EHS) Penile length Peak systolic velocity (PSV) End-diastolic velocity (EDV)	Baseline 1 month 3 months 6 months 12 months
You *et al.* (2021) (38)	Korea	A phase 1 clinical trial	Post radical prostatectomy erectile dysfunction (pRP-ED)	n=10	- Men aged 20 years or older who could not perform sexual activity (4 times) with proper sexual stimulation despite taking the maximum dose of phosphodiesterase type 5 inhibitors (PDE5Is) within the previous 8 weeks - Patients must have had a consistent partner willing to engage in sexual activity at least 2 times per month during the study - Patients with moderate to severe erectile dysfunction (ED) based on the International Index of Erectile Function (IIEF) Erectile Function domain score	- History of bone marrow disorders - Aspartate aminotransferase/alanine aminotransferase levels >3 times the upper limit of normal or creatinine levels >1.5 times the upper limit of normal - History of hypersensitivity to gentamicin - Severe cardiovascular disease (e.g., angina, arrhythmia, cardiac failure, stroke), kidney failure, or respiratory failure - Positive test for HIV, hepatitis B virus, hepatitis C virus, or syphilis - Prostate-specific antigen (PSA), carcinoembryonic antigen, or alpha-fetoprotein levels outside of the normal range - History of cancer in the previous 5 years (except prostate cancer) - Uncontrolled hypertension or hypotension (systolic blood pressure >170 mm Hg or <90 mm Hg; diastolic pressure >100 mm Hg or <50 mm Hg) - HbA1c level >10% - Receiving anticoagulant treatment. - Severe infectious disease - Testosterone level <200 ng/dL - History of penile implant or willingness to have one - Morphological changes of the penis	62.0+13.0	18.1+10.7	-	Baseline 1 month 3 months 6 months 9 months 12 months

Abbreviations: BMI: body mass index; IIEF: international index of erectile function; ED: erectile dysfunction; PDE5Is: phosphodiesterase type 5 inhibitors; HIV: human immunodeficiency virus; PSA: prostate-specific antigen; BP: blood pressure; EHS: erection hardness score; PSV: peak systolic velocity; EDV: end-diastolic velocity; RI: Resistive index; HbA1c: hemoglobin A1C; HBV: hepatitis B virus; HCV: hepatitis C virus; pRP-ED: post-radical prostatectomy erectile dysfunction; RP: radical prostatectomy; CDDU: color duplex doppler ultrasound; SD: standard deviation.

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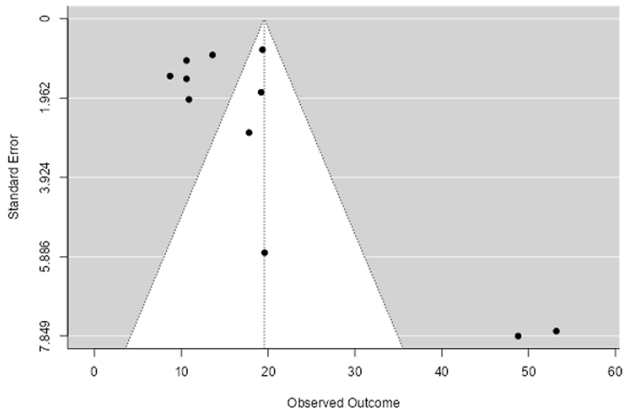

Figure S1 Funnel plot for publication bias.

Table S2 (A) Leave-one-out sensitivity analysis for IIEF results; (B) leave-one-out sensitivity analysis for PSV results

(A)			
Excluded study	Pooled effect	95% CI	I^2 (%)
None	16.87	13.31–20.43	92.6
Al Demour *et al.* (2021)	17.85	13.56–22.15	93.2
Al Demour *et al.* (2024)	17.84	13.91–21.76	92.3
Alhefnawy *et al.* (2023)	16.66	12.84–20.48	93.0
Koga and Horiguchi (2021)	16.24	12.70–19.79	89.0
Levy *et al.* (2015)	15.26	11.94–18.58	91.8
Levy *et al.* (2016)	15.49	12.09–18.89	92.3
Mirzaei *et al.* (2021)	17.76	13.89–21.63	92.9
Nguyen *et al.* (2021)	17.65	13.82–21.48	93.1
Protogerou *et al.* (2020)	16.83	13.05–20.62	93.3
Yiou *et al.* (2015)	17.84	14.11–21.57	92.2
You *et al.* (2021)	16.73	13.06–20.41	93.3
(B)			
Excluded study	Pooled effect	95% CI	I^2 (%)
None	5.85	3.36–8.34	95.0
Al Demour *et al.* (2021)	5.86	2.99–8.73	95.4
Al Demour *et al.* (2024)	5.84	2.89–8.79	95.5
Alhefnawy *et al.* (2023)	6.09	3.33–8.85	94.8
Levy *et al.* (2015)	6.36	4.14–8.58	91.8
Levy *et al.* (2016)	5.54	2.58–8.49	95.3
Mirzaei *et al.* (2021)	6.41	3.85–8.97	93.6
Protogerou *et al.* (2020)	4.44	2.67–6.21	88.7
Yiou *et al.* (2015)	5.47	2.48–8.46	95.3

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Table S3 (A) Leave-one-out sensitivity analysis for EDV results; (B) leave-one-out sensitivity analysis for EHS results; (C) leave-one-out sensitivity analysis for RI results.

(A)			
Excluded study	Pooled effect	95% CI	I^2 (%)
None	5.85	3.36–8.34	95.0
Al Demour *et al.* (2021)	5.86	2.99–8.73	95.4
Al Demour *et al.* (2024)	5.84	2.89–8.79	95.5
Alhefnawy *et al.* (2023)	6.09	3.33–8.85	94.8
Levy *et al.* (2015)	6.36	4.14–8.58	91.8
Levy *et al.* (2016)	5.54	2.58–8.49	95.3
Mirzaei *et al.* (2021)	6.41	3.85–8.97	93.6
Protogerou *et al.* (2020)	4.44	2.67–6.21	88.7
Yiou *et al.* (2015)	5.47	2.48–8.46	95.3
(B)			
Excluded study	Pooled effect	95% CI	I^2 (%)
None	1.71	0.94–2.48	90.4
Al Demour *et al.* (2021)	1.38	0.95–1.81	74.2
Al Demour *et al.* (2024)	1.81	0.84–2.78	92.5
Yiou *et al.* (2015)	1.98	1.31–2.65	86.1
(C)			
Excluded study	Pooled effect	95% CI	I^2 (%)
None	0.79	0.72–0.86	81.0
Al Demour *et al.* (2021)	0.77	0.69–0.85	79.4
Al Demour *et al.* (2024)	0.78	0.73–0.83	42.1
Mirzaei *et al.* (2021)	0.78	0.68–0.88	83.2
Yiou *et al.* (2015)	0.82	0.74–0.90	76.9

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