

Mortality Reduction in Diabetics with PDE5 Inhibitor, Statin, and Testosterone Combination

By Jeffrey Dach, MD

Complete References

1. Kashyap, Sangeeta R., et al. Insulin resistance is associated with impaired nitric oxide synthase activity in skeletal muscle of type 2 diabetic subjects. *The Journal of Clinical Endocrinology & Metabolism*. 2005;90.2: 1100-1105.
2. Tessari, Paolo, et al. Nitric oxide synthesis is reduced in subjects with type 2 diabetes and nephropathy. *Diabetes*. 2010; 59.9: 2152-2159.
3. Jeddi, Sajad, et al. Role of nitric oxide in type 1 diabetes-induced osteoporosis. *Biochemical Pharmacology*. 2021: 114888.
4. Jahn, Linda A., et al. Nitric oxide-dependent micro-and macrovascular dysfunction occurs early in adolescents with type 1 diabetes. *American Journal of Physiology-Endocrinology and Metabolism*. 2022;322.2: E101-E108.
5. Oleson, Bryndon J., and John A. Corbett. Dual role of nitric oxide in regulating the response of β cells to DNA damage. *Antioxidants & redox signaling*. 2018;29.14: 1432-1445.
6. Edmonds, Michael E., et al. Multicenter, randomized controlled, observer-blinded study of a nitric oxide generating treatment in foot ulcers of patients with diabetes—ProNOx1 study. *Wound Repair and Regeneration*. 2018;6.2: 228-237.
7. Malone-Povolny, Maggie J., Sara E. Maloney, and Mark H. Schoenfisch. Nitric oxide therapy for diabetic wound healing. *Advanced healthcare materials*. 2019; 8.12: 1801210.
8. Zhang, Pengju, et al. Copper-based metal-organic framework as a controllable nitric oxide-releasing vehicle for enhanced diabetic wound healing. *ACS Applied Materials & Interfaces*. 2020;12.16: 18319-18331.
9. Fan, Yuyan, et al. Astragaloside IV protects against diabetic nephropathy via activating eNOS in streptozotocin diabetes-induced rats. *BMC Complementary and Alternative Medicine*. 2019;19.1: 1-10.
10. Naseri, Mohsen, et al. The effect of *Melissa officinalis* L. extract on learning and memory: Involvement of hippocampal expression of nitric oxide synthase and brain-derived neurotrophic factor in diabetic rats. *Journal of Ethnopharmacology*. 2021;276: 114210.
11. Sambe, Takehiko, et al. Metformin treatment decreases nitroxidative stress, restores nitric oxide bioavailability and endothelial function beyond glucose control. *Biomedicine & pharmacotherapy*. 2018; 98: 149-156.
12. Muraleedharan, Vakkat, et al. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *European Journal of Endocrinology*. 2013;169.6: 725-733.
13. Maqbool, Mudasir, and Imran Gani. Utilization of Statins in Reducing Comorbidities of Diabetes Mellitus: A Systematic Review. *Journal of Pharmacy Practice and Community Medicine*. 2018; 4.4.
14. Zhang, Quanwu, et al. Short-term statin exposure is associated with reduced all-cause mortality in persons with diabetes. *Medical Care*. 2007: 308-314.
15. Fung, Colman Siu Cheung, et al. Statin use reduces cardiovascular events and all-cause mortality amongst Chinese patients with type 2 diabetes mellitus: a 5-year cohort study. *BMC Cardiovascular Disorders*. 2017; 17.1: 1-9.
16. Chen, Po-Hsun, et al. Effects of statins on all-cause mortality at different low-density-lipoprotein cholesterol levels in Asian patients with type 2 diabetes. *Current medical research and opinion*. 2018; 34.11: 1885-1892.



Mortality Reduction in Diabetics with PDE5 Inhibitor, Statin, and Testosterone Combination

17. Corbin, J. D. *Mechanisms of action of PDE5 inhibition in erectile dysfunction. International journal of impotence research.* 2004; 16.1: S4-S7.
18. Kass, David A., et al. Phosphodiesterase regulation of nitric oxide signaling. *Cardiovascular research.* 2007;75.2: 303-314.
19. Burnett, Arthur L. Phosphodiesterase 5 mechanisms and therapeutic applications. *The American journal of cardiology.* 2005; 96.12: 29-31.
20. Santi, Daniele, et al. Therapy of endocrine disease: effects of chronic use of phosphodiesterase inhibitors on endothelial markers in type 2 diabetes mellitus: a meta-analysis. *European journal of endocrinology.* 2015;172.3: R103-R114.
21. Anderson, Simon G., et al. Phosphodiesterase type-5 inhibitor use in type 2 diabetes is associated with a reduction in all-cause mortality. *Heart.* 2016;102.21: 1750-1756.
22. Hackett, Geoffrey, et al. Statin, testosterone and phosphodiesterase 5-inhibitor treatments and age related mortality in diabetes. *World journal of diabetes.* 2017; 8.3: 104.
23. Huang, Sharon A., and Janette D. Lie. Phosphodiesterase-5 (PDE5) inhibitors in the management of erectile dysfunction. *Pharmacy and therapeutics.* 2013;38.7: 407.
24. Indian Health Service National Pharmacy and Therapeutics Committee Formulary Brief: Phosphodiesterase 5 Inhibitors for the Treatment of Erectile Dysfunction -August 2018-
25. Gallo, Luigi, Stefano Pecoraro, and Pasquale Sarnacchiaro. Adjuvant daily therapy with L-arginine 2,500 mg and tadalafil 5 mg increases efficacy and duration of benefits of low-intensity extracorporeal shock wave therapy for erectile dysfunction: A prospective, randomized, single-blinded study with 1-year follow-up. *Investigative and Clinical Urology.* 2022;63.1: 83.
26. El-Wakeel, L. M., et al. Efficacy and tolerability of sildenafil/l-arginine combination relative to sildenafil alone in patients with organic erectile dysfunction. *Andrology.* 2020;8.1: 143-147.
27. Mirone, Vincenzo, et al. A new original nutraceutical formulation ameliorates the effect of Tadalafil on clinical score and cGMP accumulation. *Archivio Italiano di Urologia e Andrologia.* 2021; 93.2: 221-226.
28. Etminan M et al. Risk of Ocular Adverse Events Associated With Use of Phosphodiesterase 5 Inhibitors in Men in the US.
29. Pineault, Kevin, et al. Phosphodiesterase type 5 inhibitor therapy provides sustained relief of symptoms among patients with chronic pelvic pain syndrome. *Translational Andrology and Urology* 2020;9.2: 391.
30. Benelli, Andrea, et al. Once-daily 5 mg tadalafil oral treatment for patients with chronic prostatitis/chronic pelvic pain syndrome. *Therapeutic Advances in Urology.* 2018;10.12: 377-381.
31. Demirtaş, Abdullah, et al. Is Tadalafil an Effective Treatment Option for Interstitial Cystitis/Painful Bladder Syndrome? A Report of a Challenging Case. *Cureus.* 2021;13.7.
32. Hatzimouratidis, Konstantinos. A review of the use of tadalafil in the treatment of benign prostatic hyperplasia in men with and without erectile dysfunction. *Therapeutic Advances in Urology.* 2014;6.4: 135-147.
33. Singh, Sanket Narayan, et al. Comparing the effect of Alpha blocker (Silodosin) and Phosphodiesterase type 5 inhibitor (Tadalafil) in benign prostate hyperplasia patients with lower urinary tract symptoms: a single centre study. *International Surgery Journal.* 2018;5.5: 1866-1872.
34. Casabé, Adolfo, et al. Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *The Journal of urology.* 2014;191.3 (2014): 727-733.
35. Cai, Zhonglin, Jianzhong Zhang, and Hongjun Li. Two birds with one stone: regular use of PDE5 inhibitors for treating male patients with erectile dysfunction and cardiovascular diseases. *Cardiovascular Drugs and Therapy.* 2019; 33.1: 119-128.

Mortality Reduction in Diabetics with PDE5 Inhibitor, Statin, and Testosterone Combination

36. Peixoto, Christina Alves, Ana Karolina Santana Nunes, and Ana Garcia-Osta. Phosphodiesterase-5 inhibitors: action on the signaling pathways of neuroinflammation, neurodegeneration, and cognition. *Mediators of Inflammation*. 2015 (2015).
37. Peixoto, Christina A., Ana KS Nunes, and Catarina Rapôso. The role of NO/cGMP signaling on neuroinflammation: a new therapeutic opportunity. *Mechanisms of neuroinflammation*. (2017): 167-208.
38. Nabavi, Seyed Mohammad, et al. Phosphodiesterase inhibitors say NO to Alzheimer's disease. *Food and Chemical Toxicology*. 134 (2019): 110822.
39. Ben Aissa, Manel, et al. Targeting NO/cGMP signaling in the CNS for neurodegeneration and Alzheimer's disease. *Current medicinal chemistry*. 2016; 23.24: 2770-2788.
40. de Santana Nunes, Ana Karolina, et al. Sildenafil (Viagra®) prevents and restores LPS-induced inflammation in astrocytes. *Neuroscience Letters*. 2016;630: 59-65.
41. França, Maria Eduarda Rocha, et al. Tadalafil restores long-term memory and synaptic plasticity in mice with hepatic encephalopathy. *Toxicology and Applied Pharmacology*. 2019;379: 114673.
42. Hackett G. PDE5 inhibitors in diabetic peripheral neuropathy. *Int J Clin Pract*. 2006 Sep;60(9):1123-6.
43. Wang, Lei, Michael Chopp, and Zheng Gang Zhang. PDE5 inhibitors promote recovery of peripheral neuropathy in diabetic mice. *Neural regeneration research*. 2017;12.2: 218.
44. da Rocha Araújo, Shyrlene Meiry, et al. Effect of sildenafil on neuroinflammation and synaptic plasticity pathways in experimental autoimmune encephalomyelitis. *International Immunopharmacology*. 2020; 85: 106581.
45. Duarte-Silva, Eduardo, et al. Phosphodiesterase-5 inhibitors: Shedding new light on the darkness of depression? *Journal of Affective Disorders*. 2020;264: 138-149.
46. Das, Anindita, et al. PDE5 inhibitors as therapeutics for heart disease, diabetes and cancer. *Pharmacology & therapeutics*. 2015; 147: 12-21.
47. Hackett, Geoffrey. Should all men with type 2 diabetes be routinely prescribed a phosphodiesterase type 5 inhibitor? *The world journal of men's health*. 2020; 38.3: 271.
48. Maas, Renke, and Roman N. Rodionov. Phosphodiesterase-5 inhibitors and survival in men with coronary artery disease. *Journal of the American College of Cardiology*. 2021;77.12: 1551-1553.
49. Hackett, Geoffrey, et al. Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. *BJU Int*. 2019;123.3: 519-529.
50. El-Bakly, Wesam, et al. The efficacy and underlying mechanism of phosphodiesterase-5 inhibitors in preventing cognitive impairment and Alzheimer pathology: A systematic review of animal studies. *Behavioural Brain Research*. 372 (2019): 112004.
51. Sanders, Owen. Sildenafil for the treatment of Alzheimer's disease: a systematic review. *Journal of Alzheimer's Disease Reports*. 2020;4.1: 91-106.
52. Rutten, K., et al. The selective PDE5 inhibitor, sildenafil, improves object memory in Swiss mice and increases cGMP levels in hippocampal slices. *Behavioural brain research*. 2005;164.1: 11-16.
53. Xiong, Ying, and Pia Wintermark. The Role of Sildenafil in Treating Brain Injuries in Adults and Neonates. *Frontiers in Cellular Neuroscience*. 2020; 16.
54. Hackett, G. PDE5 inhibitors in diabetic peripheral neuropathy. *International journal of clinical practice*. 2006; 60.9: 1123-1126.
55. Percival, Justin M., et al. Sildenafil reduces respiratory muscle weakness and fibrosis in the mdx mouse model of Duchenne muscular dystrophy. *The Journal of pathology*. 2012;228.1: 77-87.
56. Nelson, Michael D., et al. PDE5 inhibition alleviates functional muscle ischemia in boys with Duchenne muscular dystrophy. *Neurology*. 2014;82.23: 2085-2091.
57. Andersson, Daniel P., et al. Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction. *Heart*. 12017;03.16: 1264.

Mortality Reduction in Diabetics with PDE5 Inhibitor, Statin, and Testosterone Combination

58. Yang, Han-Mo, et al. Sildenafil reduces neointimal hyperplasia after angioplasty and inhibits platelet aggregation via activation of cGMP-dependent protein kinase. *Scientific reports*. 2019; 9.1: 1-12.
59. Cruz-Burgos, Marian, et al. New approaches in oncology for repositioning drugs: the case of PDE5 inhibitor sildenafil. *Frontiers in Oncology*. 2021;11: 208.
60. Pantziarka, Pan, et al. Repurposing drugs in oncology (ReDO)—selective PDE5 inhibitors as anti-cancer agents. *ecancermedicalscience* 12 (2018).
61. DuBroff, Robert J. The statin diabetes conundrum: short-term gain, long-term risk or inconvenient truth? *BMJ Evidence-Based Medicine*. (2015).
62. Bouchonville, Matthew F., et al. Are diabetes guidelines truly evidence based? *Diabetes research and clinical practice*. 2017;127: 70-79.
63. Stief, Christian G., et al. Effects of sildenafil on cAMP and cGMP levels in isolated human cavernous and cardiac tissue. *Urology*. 2000;55.1: 146-150.
64. Corbin, J. D. Mechanisms of action of PDE5 inhibition in erectile dysfunction. *International journal of impotence research*. 2004; 16.1: S4-S7.
65. Andersson, K-E. PDE5 inhibitors—pharmacology and clinical applications 20 years after sildenafil discovery. *British journal of pharmacology*. 2018;175.13: 2554-2565.
66. Ghofrani, Hossein A., Ian H. Osterloh, and Friedrich Grimminger. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nature reviews Drug discovery*. 2006;5.8: 689-702.
67. Gerhard, Marie, et al. Aging progressively impairs endothelium-dependent vasodilation in forearm resistance vessels of humans. *Hypertension*. 1996; 27.4: 849-853.
68. Taddei, Stefano, et al. Age-related reduction of NO availability and oxidative stress in humans. *Hypertension*. 2001;38.2: 274-279.
69. Egashira, Kensuke, et al. Effects of age on endothelium-dependent vasodilation of resistance coronary artery by acetylcholine in humans. *Circulation*. 1993;88.1: 77-81.



TownsendLetter.com/get-involved

