

Sexual dysfunction

Does reducing oxidative stress offer an alternative approach to treating erectile dysfunction?



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Many research centres, including our own, have examined the close interplay in type 2 diabetes between the vascular endothelium (inflammation and dysfunction), oxidative stress and insulin resistance (Kar et al, 2009). These processes seem inexorably linked (the “common soil” hypothesis) and are high on the suspect list as principal causative factors leading to diabetes and vascular disease – including ischaemic heart disease and erectile dysfunction (ED). Given these observations, it is not surprising that researchers are now examining whether tackling any of these “newer” vascular risk factors may help to attenuate or reverse the process of ED.

In this selection of articles, Shukla and colleagues (2008) fed rabbits supplemental folic acid on the premise that reducing homocysteine levels and improving oxidative stress may enhance penile nitric oxide

formation and, in turn, enhance penile smooth muscle relaxation. Indeed, all these parameters that had been impaired by the presence of diabetes were reversed by folic acid administration.

In a similar experimental study, Angulo et al (2009) examined the effects of an antioxidant (known as AC3056 for short) on ED in diabetic rats. Again, the administration of this agent reversed ED and was associated with improved nitric oxide-mediated endothelial dysfunction.

Although they are at the experimental stage, these approaches may offer further hope of improving erectile performance, either as stand-alone therapy or augmentation of other established treatment options. However, prospective clinical studies are needed to support these proof-of-concept data, given the largely negative clinical trials associated with antioxidants aimed at improving vascular outcome.

Kar P, Laight D, Rooprai HK et al (2009) Effects of grape seed extract in type-2 diabetic subjects at high cardiovascular risk: a double-blind, randomised, placebo-controlled trial examining metabolic markers, vascular tone, inflammation, oxidative stress and insulin sensitivity. *Diabet Med* (in press)

BRITISH JOURNAL OF UROLOGY INTERNATIONAL

Folic acid improves erectile function in diabetes model

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 Homocysteine is a risk factor for cardiovascular (CV) disease, especially in men with diabetes, and may also be a risk factor for erectile dysfunction (ED).

2 Plasma homocysteine is lowered by folic acid, which improves endothelial function in people with diabetes.

3 To determine whether folic acid may improve erectile function in men with ED and diabetes, the authors studied the effect of folic acid given orally to six diabetes-induced rabbits and six non-diabetes controls daily for 4 weeks; six diabetes-induced rabbits and six non-diabetes controls received no folic acid treatment for comparison.

4 After 4 weeks the rabbits were killed to examine the effect of folic acid on cavernosal function and intrapenile oxidative stress.

5 Carbachol- and electrical field stimulated relaxation were significantly impaired in the untreated group with diabetes, compared with the controls; furthermore, this was significantly improved following folic acid treatment.

6 Folic acid reduced plasma homocysteine levels, reduced cavernosal oxidative stress associated with diabetes, conserved nitric oxide bioactivity and improved erectile function in diabetic rabbits.

7 Folic acid treatment may have a role for reversing ED in men with diabetes, as well as improving CV health.

Shukla N, Hotston M, Persad R et al (2008) The administration of folic acid improves erectile function and reduces intracavernosal oxidative stress in the diabetic rabbit. *British Journal of Urology International* **103**: 98–103

JOURNAL OF SEXUAL MEDICINE

The new antioxidant AC3056 improves ED in diabetes

Readability	✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

1 The study determined the effects of the antioxidant AC3056 on erectile function in diabetes-induced rats and on relaxation of human corpus cavernosal (HCC) tissue and penile resistance arteries (HPRA) from men with diabetes.

2 Diabetes-induced rats were allocated to different treatment regimens with 0.3% AC3056 or to control groups.

Human penile tissue biopsies were obtained from six men without diabetes and 14 with diabetes.

3 AC3056 given from the induction of diabetes completely prevented erectile dysfunction (ED); AC3056 given after 8 weeks of diabetes significantly improved erectile function.

4 AC3056 improved endothelial function in diabetic HCC tissue and improved endothelium-dependent relaxation in diabetic HPRA with significant potentiated neurogenic relaxation of both tissues.

5 Oxidative stress plays a major role in causing ED in men with diabetes.

Angulo J, Peiró C, Cuevas P et al (2009) The novel antioxidant, AC3056 (2,6-di-t-butyl-4-((dimethyl-4-methoxyphenylsilyl) methoxy) phenol), reverses erectile dysfunction in diabetic rats and improves NO-mediated responses in penile tissue from diabetic men. *J Sex Med* **6**: 373–87

JOURNAL OF SEXUAL MEDICINE

Weight loss and physical activity improve ED

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓✓

- The authors examined the effect of lifestyle changes on erectile function in men with erectile dysfunction (ED) or at risk of ED.
- In total, 104 men were randomly allocated to the intervention group and were given detailed lifestyle advice including weight loss, diet and physical activity; 105 men in the control group were given general information about their health.
- Outcome measures included change in erectile function score, as measured by the International Index of Erectile Function-5 (IIEF-5), and relationship between erectile improvement and changes in lifestyle.
- At baseline, 34% of men in the lifestyle advice group and 36% of men in the control group had normal erectile function. After 2 years, 56% of men in the intervention group and 38% of men in the control group had normal erectile function ($P=0.015$).
- Men in the intervention group were more likely to make changes to their lifestyle in terms of diet and exercise, with a strong correlation between success of intervention and restoration of erectile function.
- Improvement of erectile function can be achieved by making lifestyle changes in men with ED or at risk of ED.
- These lifestyle changes improve endothelial function and reduce insulin resistance and the low-grade inflammatory state linked with metabolic conditions, such as obesity, the metabolic syndrome and type 2 diabetes, which are risk factors of ED.

Esposito K, Ciotola M, Giugliano F et al (2009) Effects of intensive lifestyle changes on erectile dysfunction in men. *J Sex Med* **6**: 243–50

DIABETES METABOLISM RESEARCH AND REVIEWS

Sildenafil does not improve FMD

Readability	✓✓✓
Applicability to practice	✓✓✓
WOW! factor	✓✓✓

- The study investigated the effects of a single dose of sildenafil 100 mg on flow-mediated dilatation (FMD) and cardiovascular (CV) autonomic nerve function in a double-blind, placebo-controlled, crossover trial of 40 men with type 2 diabetes and no CV disease.

- There was no statistically significant effect of sildenafil on FMD in men with type 2 diabetes compared with placebo.
- Although sildenafil caused a mild decrease in blood pressure and increase in heart rate, it did not trigger a sympathetic activation or exacerbate orthostatic hypotension.
- Sildenafil did not negatively affect CV autonomic nerve function, but neither did it improve endothelial function as assessed by FMD.

Stirban A, Laude D, Elghozi J-L et al (2009) Acute effects of sildenafil on flow-mediated dilatation and cardiovascular autonomic nerve function in type 2 diabetic patients. *Diabetes Metab Res Rev* **25**: 136–43

EXPERT OPINION ON PHARMACOTHERAPY

Sildenafil improves endothelial function

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

- The study determined the effects of sildenafil 25 mg orally for 4 weeks on levels of soluble markers of endothelial function in 112 men (mean age of 60.6 years) with erectile dysfunction (ED) of vascular aetiology, alone or with comorbidities such as diabetes or the metabolic syndrome, hypertension or coronary artery disease.

- Sildenafil was shown to significantly reduce endothelin-1, nitric oxide and cyclic guanosine monophosphate levels after 4 weeks compared with baseline; erectile function was significantly improved after 4 weeks (International Index of Erectile Function-5 score increased from 13.49 ± 5.57 at baseline to 17.72 ± 5.11 after 4 weeks; $P<0.001$).

- Sildenafil 25 mg daily improves endothelial function in men with ED as indicated by the measurement of levels of some soluble markers of endothelial function (endothelin-1, nitric oxide and cyclic guanosine monophosphate).

Angelis K, Konstantinos G, Anastasios A et al (2009) The impact of daily sildenafil on levels of soluble molecular markers of endothelial function in plasma in patients with erectile dysfunction. *Expert Opin Pharmacother* **10**: 155–60

CURRENT MEDICAL RESEARCH AND OPINION

Favourable risk-benefit balance for tadalafil once-daily

Readability	✓✓✓✓
Applicability to practice	✓✓✓✓
WOW! factor	✓✓✓

- Three trials of tadalafil once-daily for the treatment of erectile dysfunction (ED) were analysed using 12-week efficacy and safety data: two involved men with ED; one comprised

- men with ED and diabetes; only results for tadalafil 2.5 or 5 mg once-daily were evaluated.
- From baseline to study end at 12 weeks, tadalafil 2.5 or 5 mg once-daily caused an increase in erectile function scores (International Index of Erectile Function) for both the men with ED and the men with ED and diabetes compared with placebo ($P<0.01$).
- Adverse events with tadalafil, such as dyspepsia, nasopharyngitis and headaches, were seen in $\leq 4\%$ of men.

Donatucci CF, Wong DG, Giuliano F et al (2008) Efficacy and safety of tadalafil once daily: considerations for the practical application of a daily dosing option. *Curr Med Res Opin* **24**: 3383–92

“Sildenafil 25 mg daily improves endothelial function in men with erectile dysfunction as indicated by the measurement of levels of some soluble markers of endothelial function (endothelin-1, nitric oxide and cyclic guanosine monophosphate).”