

Sexual dysfunction



Does metformin affect sexual dysfunction?

Mike Cummings

Consultant Physician and Honorary Professor, Queen Alexandra Hospital, Portsmouth

At the European Association for the Study of Diabetes' meeting in September 2016, I was privileged to attend a wonderful session titled "Metformin: Oldie but goodie", during which metformin's mechanism of action, benefits and potential side effects were discussed. The likely cardiovascular benefits were summarised. These included potentially reduced cardiovascular events in type 2 diabetes (conflicting reports), reductions in blood pressure unrelated to weight loss, improvements in lipid profile and endothelial function, reductions in fibrinogen and possible increases in fibrinolysis (Sreekumaran Nair, 2016).

We also heard about the potential for anti-oncogenic effects. Observational studies have shown benefits for breast, colon, prostate and hepatocellular cancers, with evidence suggesting that metformin reduces proliferation of cancer cells *in vitro*. Metformin may even have anti-ageing effects, as evidenced by its ability to increase longevity in microbes, worms and some mammals.

There was no reference, however, to the potential impact of metformin upon sexual function. Two recent publications raise the question whether metformin may indeed be associated with sexual health, each with contrasting findings. In the first (summarised alongside), Al-Kuraishy and colleagues report that metformin is associated with a significant reduction in testosterone levels and sex drive, and the induction of low-testosterone-induced erectile dysfunction. By contrast, sulfonylureas were associated with significant improvement in these parameters.

These findings are consistent with previous

evidence showing that metformin inhibits cytochrome P450 c17a, a key enzyme in testosterone synthesis that reduces luteinising hormone secretion (Valsamakis et al, 2013) and modulates leptin secretion (Ozata et al, 2001), which affects testosterone production.

In the second study (also summarised), Krysiak and colleagues report that metformin treatment normalised low sexual desire and sexual satisfaction in women with type 2 diabetes and prediabetes. The drug also normalised or improved some domains of the Female Sexual Function Index in women with diabetes; this effect was correlated with an improvement in insulin resistance. The authors cite a number of postulated mechanisms, which include the favourable effect on the hormonal milieu and insulin sensitivity.

So the findings of these studies are somewhat contrasting, and their interpretation suffers from a number of confounding factors and small sample sizes (less than 100). However, they serve to remind us that the effects upon sexual function (perhaps the most common complication in diabetes) of one of the most widely used glucose-lowering therapies are not well studied. How often have you asked your patients with diabetes about the impact of metformin on their sex life? ■

Ozata M, Oktenli C, Bingol N, Ozdemir IC (2001) The effects of metformin and diet on plasma testosterone and leptin levels in obese men. *Obes Res* **9**: 662–7

Sreekumaran Nair K (2016) Do we understand the mechanism of metformin action? Presented at: 52nd Annual Meeting of the European Association for the Study of Diabetes (oral presentation S16.1). Munich, Germany, 12–16 September

Valsamakis G, Lois K, Kumar S, Mastorakos G (2013) Metabolic and other effects of pioglitazone as an add-on therapy to metformin in the treatment of polycystic ovary syndrome (PCOS). *Hormones (Athens)* **12**: 363–78

J Clin Diagn Res

Roles of metformin and sulfonylurea in ED in men with T2D

Readability ////

Applicability to practice ///

WOW! Factor ///

- 1 Men with T2D may have low testosterone levels, which can lead to low sex drive and erectile dysfunction (ED).
- 2 This Iraqi study assessed ED and sex drive in relation to serum testosterone levels in men with T2D. Additionally, it investigated the possible roles of metformin and a sulfonylurea (SU; glibenclamide) in these changes.
- 3 A cohort of men ($n=64$) with an age range of 41–49 years with established T2D and no other complications were recruited. They were grouped according to their treatment with metformin ($n=34$) or SU ($n=30$). A cohort group of men without diabetes ($n=27$) acted as a control group. All were followed for 1 month.
- 4 Of those with T2D, 75% ($n=48$) had ED. Of these, 20 responded to sildenafil, while 28 did not. A greater proportion of those in the metformin group had ED compared to the SU group (88.2% vs 60.0%).
- 5 Total testosterone, free testosterone and bioavailable testosterone levels in the SU group were all higher than in the metformin group, but lower than in the control group. Sex hormone-binding globulin levels were also significantly higher in the SU group compared with the metformin group, as was the free androgenic index.
- 6 The authors concluded that metformin in T2D significantly reduces testosterone levels and sex drive, and increases low-testosterone-induced ED. SU significantly improves these parameters.

Al-Kuraishy HM, Al-Gareeb AI (2016) Erectile dysfunction and low sex drive in men with type 2 DM: the potential role of diabetic pharmacotherapy. *J Clin Diagn Res* **10**: FC21–6

Exp Clin Endocrinol Diabetes

Metformin and sexual function

Readability ////
 Applicability to practice ////
 WOW! Factor ////

- This study investigated the effects of metformin on sexual function and depressive symptoms in women with prediabetes and T2D.
- A total of 67 pre-menopausal women were recruited and provided with lifestyle modification advice relating to weight loss and diet.
- Women with T2D were treated with metformin (group A; $n=22$) for 6 months. Women with prediabetes were allocated to either metformin (group B; $n=23$) or no treatment (group C; $n=22$).
- Plasma glucose levels and insulin sensitivity were measured at the start and end of the study. Sexual function and depressive symptoms were evaluated using the Female Sexual Function Index (FSFI) and Beck Depression Inventory (BDI-II), respectively.
- At baseline, group A had the lowest total FSFI score and lower scores in all six domains. Groups B and C had lower scores for two domains compared with healthy controls. Scores correlated with degree of insulin resistance. BDI-II scores were higher in groups A, B and C compared to controls.
- At 6 months, metformin normalised sexual desire and sexual satisfaction in groups A and B, and improved the remaining FSFI domains in group A. These effects were correlated with improvements in insulin resistance. Metformin treatment reduced BDI-II score in group A, but not significantly.
- Metformin produces a beneficial effect on female sexual function, with the strength of the effect depending on degree of insulin resistance.

Krysiak R, Drosdzol-Cop A, Skrzypulec-Plinta, Okopien B (2017) Sexual functioning and depressive symptoms in women with diabetes and prediabetes receiving metformin therapy: a pilot study. *Exp Clin Endocrinol Diabetes* **125**: 42–8

Andrologia

Metabolic syndrome: Effects of tadalafil on ED and testosterone

Readability ////
 Applicability to practice ////
 WOW! Factor ////

- Testosterone has an important role in the modulation of erectile function in men. Low testosterone levels and erectile dysfunction (ED) are both strongly associated with the metabolic syndrome.
- This prospective, multicentre study evaluated the efficacy of the phosphodiesterase-5 inhibitor tadalafil on testosterone levels in men with ED accompanied by metabolic syndrome.
- Men with three or more criteria for metabolic syndrome were assessed for ED using the International Index of Erectile Function (IIEF)-5 questionnaire. Those with moderate and mild-to-moderate ED ($n=40$) were included in the study. Serum testosterone, follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels were also evaluated.
- After 3 months of treatment with tadalafil 5 mg once daily, significant improvements from baseline were recorded for mean testosterone levels (from 3.6 ng/mL to 5.2 ng/mL) and IIEF scores (from 11.3 to 19.0; both $P<0.05$).
- Serum LH levels decreased significantly, whereas FSH levels were unchanged.
- These results suggest that normalisation of testosterone levels by treatment with tadalafil 5 mg once daily may help to improve erectile response in men with ED and low testosterone accompanied by metabolic syndrome.
- The authors suggest that further large-scale studies in hypogonadal men are needed to provide more detailed information.

Ozcan L, Polat EC, Kocaaslan R et al (2017) Effects of taking tadalafil 5 mg once daily on erectile function and total testosterone levels in patients with metabolic syndrome. *Andrologia* **2017**: e12751

Diabetologia

Small-fibre neuropathy in men with T1D and ED

Readability ////
 Applicability to practice ////
 WOW! Factor ////

- This cross-sectional study aimed to identify the contribution of small- and large-fibre neuropathy to erectile dysfunction (ED) in men with T1D.
- The investigators assessed 70 consecutive men with T1D (29 without and 41 with ED) from a UK diabetes centre and 34 age-matched healthy volunteers. The participants underwent a comprehensive assessment of small- and large-fibre neuropathy using variety of tests, including corneal confocal microscopy (CCM).
- ED was found in 58.6% of men with T1D compared to 5.9% in the control group.
- After adjusting for age, individuals with T1D and ED had significantly worse scores on the Neuropathy Symptom Profile and other measures of neuropathy compared to those without ED. This was particularly evident in the results for small-fibre and autonomic neuropathy.
- The study demonstrated widespread small-fibre damage in men with T1D and ED. CCM was shown to be an objective and non-invasive technique for quantifying small-fibre damage.
- The diagnosis and management of ED in men with diabetes is challenging, but the identification of more extensive small-fibre damage using CCM may allow those who are less likely to respond to conventional therapies for ED, such as phosphodiesterase-5 inhibitors, to be identified.

Azmi S, Ferdousi M, Alam U et al (2017) Small-fibre neuropathy in men with type 1 diabetes and erectile dysfunction: a cross-sectional study. *Diabetologia* **60**: 1094–101

“These results suggest that normalisation of testosterone levels by treatment with tadalafil 5 mg once daily may help to improve erectile response in men with erectile dysfunction and low testosterone accompanied by metabolic syndrome.”