

Sexual dysfunction

Idiopathic hypogonadism with glucose-lowering therapy?



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Hypogonadism is now a much more recognised finding in men with T2D than previously thought (Dhindsa et al, 2004), perhaps affecting 30% of men with the condition. The classical finding is that of so-called “eugonadotropic hypogonadism” with leutinising hormone (LH) levels in the normal range associated with a low concentration of circulating active testosterone. The condition may be associated with fairly insidious symptoms including reduced libido and erectile dysfunction accompanied by a modest reduction in testosterone levels, whilst the classical findings of reduced body hair and secondary sexual characteristics tend to be confined to far less common cases of severe hypogonadism. The precise mechanisms that promote the development of hypogonadism in people with diabetes are not fully understood. However, the impact of increased adiposity resulting in greater inhibitory effects of cytokines and other chemical mediators that feedback upon the hypothalamus are thought to play a pivotal role. Other factors have been implicated and the study by Sridhar

and colleagues (summarised alongside) raises the possibility that a commonly used glucose-lowering agent, pioglitazone, may contribute to hypogonadism. In their study, they examined the testosterone axis in men with diabetes receiving pioglitazone (30 mg/day) versus placebo and demonstrated a statistically significant drop of 1.2 nmol/L in total testosterone levels (0.06 nmol/L drop in calculated free testosterone levels) with pioglitazone therapy, whereas LH levels remained unchanged. Potential mechanisms include improved insulin sensitivity or a direct effect upon steroidogenesis (Romualdi et al, 2003). The study employed a low sample size ($n=50$) with pre-determined eugonadism and the absolute drop in testosterone concentration may not be of any clinical significance. However, in a sub-group of people with diabetes who are susceptible to hypogonadism, further evaluation and consideration are justified.

“Other factors have been implicated and the study by Sridhar and colleagues raises the possibility that a commonly used glucose-lowering agent, pioglitazone, may contribute to hypogonadism.”

Dhindsa S, Prabhakar S, Sethi M et al (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. *J Clin Endocrinol Metab* **89**: 5462–8

Romualdi D, Guido M, Ciampelli M et al (2003) Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. *Hum Reprod* **18**: 1210–8

J SEX MED

FSD and diabetes

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

1 The authors performed a meta-analysis to determine the frequency of female sexual dysfunction (FSD) and its clinical correlates in women with diabetes. MEDLINE, EMBASE and Cochrane Library were systematically searched to identify 3168 women with diabetes and

2823 controls without diabetes for inclusion.

2 FSD was more frequent in women with T1D (odds ratio [OR] 2.27; 95% CI, 1.23–4.16) and T2D diabetes (OR 2.49; 95% CI, 1.55–3.99) compared to controls. Low Female Sexual Function Index was associated with high BMI ($P=0.005$).

3 The authors concluded that FSD is more common in women with diabetes.

Pontiroli AE, Cortelazzi D, Morabito A (2013) Female sexual dysfunction and diabetes. *J Sex Med* **10**: 1044–51

CLIN ENDOCRINOL (OXF)

Does pioglitazone lower testosterone in men with T2D?

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

1 Pioglitazone acts as an insulin sensitiser and is often prescribed in the management of T2D. Although pioglitazone is known to lower testosterone in women with polycystic ovarian syndrome, there is little evidence examining its effect on testosterone levels in men.

2 The authors performed a randomised, double-blind controlled trial to evaluate the effects of pioglitazone on testosterone levels in eugonadal men aged 30–35 years with T2D.

3 Participants already prescribed metformin and glimepiride were randomised to receive 30 mg of pioglitazone ($n=25$) per day or placebo ($n=25$) for 6 months.

4 Mean total testosterone level ($P=0.031$), calculated free testosterone ($P=0.001$) and bioavailable testosterone ($P=0.000$) were significantly reduced after 6 months of pioglitazone therapy compared to placebo, whereas sex hormone-binding globulin levels significantly increased ($P=0.000$).

5 Pioglitazone therapy was also associated with increased plasma androstenedione ($P=0.051$). Reduced testosterone levels were independent of alterations in HbA_{1c}, body weight and body fat.

6 The authors concluded that total, free and bioavailable testosterone were significantly decreased with the use of pioglitazone in this cohort of eugonadal men with T2D, although the long-term effects of these reductions require further investigation.

Sridhar S, Walia R, Sachdeva N et al (2013) Effect of pioglitazone on testosterone in eugonadal men with type 2 diabetes mellitus: a randomized double-blind placebo-controlled study. *Clin Endocrinol (Oxf)* **78**: 454–9

J SEX MED

Folic acid and tadalafil as combination therapy for ED

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

1 Phosphodiesterase type 5 inhibitors (PDE5Is) are often prescribed to men with erectile dysfunction (ED), although previous evidence suggests that this class of drugs may be less effective in men with T2D.

2 The aim of this study was to investigate the efficacy and tolerability of tadalafil and folic acid as combination therapy for ED in men with T2D.

3 As a part of this double-blind clinical trial, participants ($n=83$) were randomised to receive either tadalafil (10 mg) every 2 days and folic acid (5 mg) daily (group A) or tadalafil every 2 days and placebo daily (group B).

4 International Index of Erectile Function (IIEF) scores were recorded at baseline and after 3 months. In both groups, mean IIEF scores were higher after treatment compared to before ($P<0.001$).

5 Participants from group A displayed a significantly higher mean IIEF score compared with those from group B ($P<0.001$). No incidences of withdrawal due to adverse reactions were reported throughout the study period.

6 The authors concluded that folic acid and tadalafil were well tolerated in the study cohort. A significant improvement in sexual function was associated with the combined use of folic acid and tadalafil in this group of men with ED and T2D.

Hamidi Madani A, Asadolahzade A, Mokhtari G et al (2013) Assessment of the efficacy of combination therapy with folic acid and tadalafil for the management of erectile dysfunction in men with type 2 diabetes mellitus. *J Sex Med* **10**: 1146–50

CLIN ENDOCRINOL (OXF)

Kisspeptin-10 may increase LH and testosterone secretion

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

1 The authors aimed to determine the effects of the exogenous neuropeptide kisspeptin-10 on luteinising hormone (LH) and testosterone production in hypotestosteronaemic men

with ($n=5$) and without T2D ($n=7$).

2 Following the administration of intravenous kisspeptin-10 (0.3 mcg/kg bolus), mean LH increased in all participants ($P<0.001$ and $P=0.02$ respectively). Elevated testosterone levels were reported in men with T2D ($P=0.05$), who also displayed a greater LH pulse frequency ($P=0.002$).

3 The authors concluded that increased testosterone and LH production were observed in response to kisspeptin-10 administration.

George JT, Veldhuis JD, Tena-Sempere M et al (2013) Exploring the pathophysiology of hypogonadism in men with type 2 diabetes. *Clin Endocrinol (Oxf)* **79**: 100–4

“A significant improvement in sexual function was associated with the combined use of folic acid and tadalafil in this group of men with erectile dysfunction and T2D.”

ANDROLOGY

Retrograde ejaculation is common in diabetes

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

1 A prospective, blinded case-control study was conducted to establish the prevalence of retrograde ejaculation (RE) in men with diabetes.

2 Out of 26 participants with diabetes, nine individuals had RE, whereas no members of

the control group were diagnosed with RE ($n=16$; $P<0.01$).

3 Participants with RE and diabetes were reported to be less sexually satisfied compared to controls. A higher rate of erectile dysfunction was observed in men with RE and diabetes compared to people without diabetes, and individuals with diabetes but not RE.

4 The authors concluded that RE is common amongst men with diabetes, as one out of three people with diabetes were identified as having RE.

Fedder J, Kaspersen MD, Brandslund I et al (2013) Retrograde ejaculation and sexual dysfunction in men with diabetes mellitus. *Andrology* **4**: 602–6

UROLOGY

Tight glycaemic control may improve Peyronie’s disease symptoms

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

1 The aim of this study was to retrospectively analyse the relationship between glycaemia and Peyronie’s disease (PD) symptoms.

2 Plaque area and pain were assessed in 36 non-smoking males with uncompensated diabetes before and after

the initiation of antidiabetic therapy.

3 After 37 ± 13 weeks of treatment, plaque area and pain levels were reduced. A significant correlation between glycaemia before treatment and the percentage decrease in plaque size was found in men with diabetes ($P=0.0002$). Control participants ($n=32$), however, who had their PD symptoms assessed at a mean time lag of 39 ± 11 weeks after treatment initiation, displayed a significantly increased plaque area and unaltered pain levels.

4 The authors concluded that diabetes compensation is essential in the management of PD.

Cavallini G, Paulis G (2013) Improvement of chronic Peyronie’s disease symptoms after diabetic compensation. *Urology* **81**: 794–8