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SEXUAL MEDICINE

Increased PDE5 levels in a mouse model of type 2 diabetes

Type 2 diabetes is a known risk factor for the development of erectile dysfunction (ED), and diabetic men often have a more severe form of ED, as well as being unresponsive to the standard treatment of phosphodiesterase type 5 (PDE5) inhibitors. In men with diabetes, the PDE5-inhibitor response rate is around 50%—much lower than in the general population. Previous studies have suggested that diabetes is associated with impaired vasodilatation in response to PDE5; however, the mechanisms of this effect are not well understood. A study in the *Journal of Sexual Medicine* has now sought to elucidate the mechanisms of diabetes-associated ED.

A team from the University of Virginia used a mouse model of type 2 diabetes—animals fed a high fat diet (HFD)—as opposed to the commonly-used streptozocin (STZ)-induced diabetic model, which is a better model for type 1 diabetes.

Glucose tolerance testing, intracorporal pressure (ICP) measurements, oxidative stress, apoptosis, PDE5, p53 and cGMP levels were measured at baseline and again at 22–36 weeks in HFD and control mice. STZ-induced diabetic mice were also used as a second control group.

Glucose tolerance testing confirmed the presence of diabetes in the HFD-fed mice. Furthermore, ICP measurements in response to cavernous nerve electrostimulation, which were similar at baseline, were significantly reduced in HFD-fed mice compared with chow-fed mice, confirming altered erectile function. Mice fed an HFD also displayed more intense staining for DHE, a marker of oxidative stress, in corporal tissue and an increase in apoptotic cells. In concordance with this result, levels of p53—a protein implicated in apoptosis—were increased by 41% in HFD-fed mice compared with chow-fed controls.

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However, the most interesting observation concerned levels of PDE5 and cyclic guanosine monophosphate (cGMP). PDE5 was increased by 41% in HFD-fed diabetic mice compared with controls, providing a potential reason why PDE-inhibitors are less effective in diabetic men. This increase was compounded by a 67% decrease in cGMP in corporal tissues. By contrast, STZ-induced type 1 diabetic mice showed decreased levels of PDE5.

"The observation that PDE5 levels are elevated in these mice fed an HFD may aid in explaining the poor response rates in diabetic humans with ED and a finding that would have been missed if studies remained restricted to type 1 diabetes," Lysiak told *Nature Reviews Urology*.

The authors believe that this is the first time such a mechanism has been demonstrated in type 2 diabetic mice, and could open up new avenues of investigation for men with diabetes and ED.

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Original article Ellati, R. D. *et al.* Increased phosphodiesterase type 5 levels in a mouse model of type 2 diabetes mellitus. *J. Sex. Med.* doi:10.1111/j.1743-6109.2012.02854.x