



Editorial – referring to the article published on pp. 940–947 of this issue

Rationale for Androgens and Erectile Dysfunction in 2006

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Erectile function (EF) is a critical and complex neurovascular process mediated by several biochemical and physiologic factors. Good erections need a good health status because the balance between the effects of vasorelaxing and vasoconstricting agents depends on the integrity of neural, vascular, and endocrine systems. There is much debate as to the benefits and risks of treating androgen deficiency in the ageing male and long-term studies are underway to answer many of these questions. In this issue of *European Urology*, Greco and coworkers retrospectively review the scientific literature on combination therapy with androgens and phosphodiesterase type 5 inhibitors (PDE5-Is) for the treatment of erectile dysfunction (ED) [1].

The topic is complicated and always debated as to the role of androgens in penile erection. Although testosterone clearly has an impact on sexual desire in humans, a direct effect on penile tissues is less clear. Several studies have pointed to the impact of androgens on penile development as well as on penile function. Most of the available data come from preclinical animal models, but they have provided important data on the biochemical and physiologic action of androgens in ED. We are not aware of the minimal testosterone threshold required for maintaining EF and a wide range of individual thresholds are known for partial androgen-deficiency symptoms in men. Different aspects of male sexual behaviour could be responsive to different testosterone threshold levels [2]. Testosterone thresholds could also be lower for

sexually motivated activity in humans. In the penis, it has been reported that dihydrotestosterone (DHT) seems to be the critical hormone in maintaining EF because of its higher binding affinity to the androgen receptor (AR) [3]. The androgen pathway involves steroid binding to the AR. But the polymorphism of those ARs, with different lengths of sequences (repeat glutamine [CAG] or glycine [GGC]), influences the function of androgenisation to the target tissues. The ARs with fewer CAG repeats are thought to mediate a stronger androgen action than the same receptor with longer CAG repeats. This remains a matter of debate and is an area that needs to be explored further.

However, the role of testosterone in modulating erectile physiology is controversial. Recent studies in humans have been translated from animal findings and are promising. Aversa and coworkers showed that men with ED and low free testosterone levels may have an impaired relaxation of the penile smooth muscle [4]. Guay and coworkers reported in a corollary that decreased testosterone levels progressively restrict the responsiveness of PDE5-I treatment [5]. These clinical data are supported by the recent study of Zhang and coworkers who showed that administration of androgens in androgen-deficient rodents facilitates the action of PDE5-Is [6]. Mulhall and coworkers have concluded in hypogonadic men with ED that the normalisation of serum testosterone levels was only associated with a short-term period of EF improvement [7]. It has also been suggested

that testosterone is important for EF but that probably other androgen-independent pathways could be involved.

ED increases with age. But the prevalence and severity of ED can also be correlated with a multitude of others factors such as diabetes, high blood pressure, hyperlipidaemia, and cardiovascular disease. Testosterone level and bioavailability decline with age due to modification in the hypothalamic-pituitary-testicular axis. The function of ARs may also be altered with age and this may lead to higher testosterone threshold levels required for EF in older men.

The androgen-dependent regulation of nitric oxide synthase (NOS) in the corpus cavernosum of animal models is now well reported [8]. Several reports have also shown that androgen deficiency results in decreased expression and activity of PDE5 [6,8]. As reported by Greco and coworkers in this issue of *European Urology*, such observations in animal models suggest the link between androgens and the regulation of signaling pathways and several structures in penile tissue [1].

Few studies reported the role of androgens in endothelial wall integrity. Vascular endothelium dysfunction leads to atherogenesis with macrophage infiltration but this mechanism is poorly defined in corpus cavernosum. ED is often associated with endothelial dysfunction. The PDE5-Is seem to improve endothelial function with chronic administration [9]. Rogers and coworkers showed that androgen deficiency could impair vascular endothelial growth factor (VEGF) synthesis and promote transforming growth factor β 1 (TGF- β 1) and connective tissue growth factor (CTGF), leading to decreased smooth muscle fibers [10]. Clinical data published so far in the literature strongly suggest the impact of androgens in maintaining human EF. They could have a major role in the balance between autocrine and paracrine growth factor production. Again additional basic and clinical research is mandatory to support these arguments.

Ten to 20% of patients with ED have low to low-normal testosterone levels. Thresholds need to be more precisely defined considering the wide variations with age to maintain sexual function and specifically EF. Jain and coworkers evaluated the effects of testosterone therapy in men with ED with 57% showing improved EF [11]. However, results are inconsistent across trials and the pooled estimate often is not significant. The problem of salvaging patients refractory to oral therapy is present in at least 30–40%. They are naturally reluctant to

take the step to intracavernous injections or such treatment might be inappropriate. Several international trials are ongoing in men with ED in whom PDE5-Is have failed, to confirm previous studies combining PDE5-Is and testosterone supplementation.

The adequate testosterone levels for effectiveness of PDE5-Is and the testosterone level used as a predictive factor for true hypogonadism in patients with low to low-normal testosterone levels remain unresolved. Diagnostic and treatment recommendations for patients with ED are the same as for men with classic androgen deficiency. Men with sexual dysfunction should be evaluated for the underlying causes, including low testosterone levels. A better understanding of the relationship between androgens and sexual behaviour will improve the treatment of ED in men with androgen deficiency to enhance their quality of life.

References

- [1] Greco EA, Spera G, Aversa A. Combining testosterone and PDE5 inhibitors in erectile dysfunction: basic rationale and clinical evidences. *Eur Urol* 2006;50:940–7.
- [2] Gray P, Singh A, Woodhouse L, et al. Dose-dependent effects of testosterone on sexual function, mood and visuospatial cognition in older men. *J Clin Endocrinol Metab* 2005;90:3838–46.
- [3] Lugg J, Rajfer J, Gonzalez-Cadavid N. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. *Endocrinology* 1995; 136:1495–501.
- [4] Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol* 2003;58:632–8.
- [5] Guay AT, Perez JB, Jacobson J, Newton RA. Efficacy and safety of sildenafil citrate for treatment of erectile dysfunction in a population with associated organic risk factors. *J Androl* 2001;22:793–7.
- [6] Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. *Eur Urol* 2005;47: 409–16.
- [7] Mulhall JP, Valenzuela R, Aviv N, Parker M. Effect of testosterone supplementation on sexual function in hypogonadal men with erectile dysfunction. *Urology* 2004;63:348–52.
- [8] Traish AM, Park K, Dhir V, Kim NN, Moreland RB, Goldstein I. Effects of castration and androgen replacement on erectile function in a rabbit model. *Endocrinology* 1999; 140:1861–8.
- [9] Rosano G, Aversa A, Vitale C, Fabbri A, Fini M, Spera G. Chronic treatment with tadalafil improves endothelial

function in men with increased cardiovascular risk. *Eur Urol* 2005;47:214-20.

[10] Rogers R, Graziottin T, Lin C, Kan Y, Lue T. Intracavernosal vascular endothelial growth factor (VEGF) injection and adeno-associated virus-mediated VEGF gene therapy pre-

vent and reverse venogenic erectile dysfunction in rats. *Int J Impot Res* 2003;15:26-37.

[11] Jain P, Rademaker A, McVary K. Testosterone supplementation for erectile dysfunction: results of a meta-analysis. *J Urol* 2000;164:371-5.