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TOPIC PAPER

G. R. Dohle · M. Smit · R. F. A. Weber

Androgens and male fertility

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Abstract Androgens play a crucial role in the development of male reproductive organs such as the epididymis, vas deferens, seminal vesicle, prostate and the penis. Furthermore, androgens are needed for puberty, male fertility and male sexual function. High levels of intratesticular testosterone, secreted by the leydig cells, are necessary for spermatogenesis. Intratesticular testosterone is mainly bound to androgen binding protein and secreted into the seminiferous tubules. Inside the sertoli cells, testosterone is selectively bound to the androgen receptor and activation of the receptor will result in initiation and maintenance of the spermatogenic process and inhibition of germ cell apoptosis. The androgen receptor is found in all male reproductive organs and can be stimulated by either testosterone or its more potential metabolite dihydrotestosterone. Severe defects of the androgen receptor may result in abnormal male sexual development. More subtle modulations can be a potential cause of male infertility. Treatment of an infertile man with testosterone does improve spermatogenesis, since exogenous administrated testosterone and its metabolite estrogen will suppress both GnRH production by the hypothalamus and Luteinising hormone production by the pituitary gland and subsequently suppress testicular testosterone production. Also, high levels of testosterone are needed inside the testis and this can never be accomplished by oral or parenteral administration of androgens. Suppression of testosterone production by the leydig cells will result in a deficient spermatogenesis, as can be seen in men taking anabolic-androgenic steroids. Suppression of spermatogenesis by testosterone administration is also the basis for the development of a male contraceptive. During cytotoxic treatment or irradiation suppression of intratesticular testosterone production cells may prevent irreversible damage to the spermotogonial stem cells.

Keywords Androgens · Male infertility · Spermatogenesis · Testicular development · Anabolic steroids

G. R. Dohle (✉)
Department of Urology,
Erasmus University Medical Center,
P.O. Box 2040, 3000 CA Rotterdam,
The Netherlands
E-mail: G.R. Dohle@erasmusmc.nl
Tel.: +31-10-4633132
Fax: +31-10-4635838

M. Smit · R. F. A. Weber
Department of Andrology,
Erasmus University Medical Center,
Rotterdam, The Netherlands

Androgens produced by the testis and the adrenal glands play a pivotal role in male reproductive and sexual function. Androgens are also needed for muscle formation, body composition, bone mineralisation, fat metabolism and cognitive functions. Low levels of testosterone or deficient action of the androgen receptor may impair male development and reproduction. Although hormonal regulation of spermatogenesis is still not completely understood, testosterone plays an essential role. A better understanding of the regulation of spermatogenesis may provide new treatment strategies for male infertility and contraception. In this review we will discuss the role of testosterone and its metabolite dihydrotestosterone (DHT) in the development and function of male reproductive organs. Indications for androgen therapy and androgen deprivation are also being discussed.

Testosterone and male sexual development

Male sexual development starts between the 7th and 12th week of gestation. The undifferentiated gonads develop into a foetal testis by expression of the sex region of the Y chromosome (SRY), a gene complex located on the short arm of the Y chromosome [18]. The

foetal testis produces two hormones: testosterone and anti-muellerian hormone (AMH). Testosterone is needed for the development of the Wolffian ducts, resulting in formation of epididymis, vas deferens and seminal vesicle. AMH-activity will result in regression of the Muellerian ducts. Under the influence of intratesticular testosterone, the number of gonocytes per tubule will increase threefold in the first months of pregnancy.

Furthermore, testosterone is needed for development of the prostate, the penis and the scrotum. However, in these organs testosterone is converted into the more potent metabolite DHT by the enzyme 5-alpha reductase. The enzyme is absent in the testes, which explains the fact that 5-alpha reductase inhibitors have no marked effect on spermatogenesis. Individuals with deficient 5-alpha reductase activity display male pseudohermaphroditism and develop a syndrome called pseudovaginal perineoscrotal hypospadias, an incomplete virilisation of the male external genitalia [27]. For penile growth, both testosterone and DHT are required. However, the androgen receptor (AR) in the penis will disappear after puberty and testosterone suppletion in adults will not result in extra penile growth [1].

Testosterone can also be metabolised into estradiol by aromatase, present in fatty tissue, the prostate and in bone. Although aromatase is also found inside the testis, the role of estrogens in the tubular compartment is unknown. An effect of estrogens on the production of Inhibin-B secretion by the sertoli cells has been suggested. Also, estrogenic action is likely to be important for leydig cell, sertoli cell and germ cell development and function [16].

The production of testosterone is controlled by Luteinising Hormone (LH) from the pituitary gland. Directly after birth, serum testosterone levels reach adult concentrations during several months. Thereafter and until puberty, testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotrophins, initiated by GnRH secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis.

Testosterone and spermatogenesis

Initiation of spermatogenesis occurs under the influence of Follicle Stimulating Hormone (FSH) after puberty [10]. The FSH-receptor is exclusively found on the surface of the sertoli cells. During foetal life, FSH is necessary for sertoli cell proliferation. Conflicting data exists on the role of FSH in spermatogenesis in humans, although a dual action of both FSH and intratesticular testosterone seems mandatory for complete quantitative and qualitative spermatogenesis [7, 14]. Upon maturation, the responsiveness for FSH of the sertoli cells diminishes and switches to an increased responsiveness for androgens [20].

Testosterone is needed for the maintenance of the spermatogenic process and for inhibition of germ cell apoptosis [21]. The seminiferous tubules of the testes are exposed to concentrations of testosterone 25–100 times greater than circulating levels. Suppression of gonadotrophins results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis [22]. Complete inhibition of intratesticular testosterone, however, results in a full arrest of meiosis up to the level of spermatids [28, 12]. Testosterone does not seem to act directly on the germ cells, but functions through the sertoli cells by expression of the androgen receptor (AR) and influencing the tubular microenvironment. Inside the tubular compartments, a multitude of paracrine factors such as peptide growth factor, cytokines, activins and many others are found. It is not yet clear if and how testosterone regulates or influences these intercellular modifying activators [14].

From animal studies it is clear that epididymal function is also androgen dependent [26]. Substantial quantities of testosterone reach the epididymis through the tubular system. For the development of the epididymis from the Wolffian ducts, testosterone is essential, but for its function in adulthood, DHT is required. The synthesis of most epididymal proteins is upregulated by androgens. During androgen deprivation the epididymis will gradually lose its ability to sustain the process of sperm maturation [3].

Testosterone inhibits both GnRH production and gondotrophins, together with its metabolite estradiol. The negative feedback hormone for FSH is Inhibin-B, produced by the sertoli cells.

Testosterone is synthesized by the leydig cells in the interstitial compartment of the testis and is mainly bound to androgen binding protein (ABP), produced by the sertoli cells. It was postulated that ABP is required for maintaining high levels of testosterone inside the tubular compartment, since there is a lack of storage capacity inside the seminiferous tubules. Also, there is no 5-alpha reductase present in the testes and therefore no DHT is produced. DHT is much more potent in binding to the AR and, therefore, much lower levels of testosterone are required in most male reproductive organs for normal development and function. It has been suggested that absence of 5-alpha reductase in the testis is compensated by high levels of intratesticular testosterone to ensure AR expression [25].

The androgen receptor

Testosterone exerts its action through the androgen receptor, located in the cytoplasm and nucleus of the target cells. Androgen binding will result in DNA activation and transcription of several proteins, with different intercellular modifying activities.

Testosterone in the foetal testis will increase the number of androgen receptors by increasing the number of cells with the AR, but also by increasing the number

of ARs in each individual cell [1]. FSH-receptor binding results in upregulation of the AR expression, which will increase the production of tubular fluid and ABP [20].

The AR-gene is found on the X chromosome (Xq 11–12) and consists of eight exons. Defects and mutations of the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation. Less severe mutations of the AR gene may cause mild forms of androgen resistance and male infertility [2]. In exon 1 of the gene, the transactivation domain consists of a trinucleotide (cytosine-adenine-guanine, CAG) tract of variable length. A variable increased length in numbers of the CAG triplets repeats was found in patients with spinobulbar muscular atrophy, also known as Kennedy disease. This X chromosome linked neuro-degenerative disease is characterised by paralysis, muscular atrophy, gynecomastia and endocrine abnormalities [9]. Since patients with this disease display a late onset androgen resistance with gynecomastia and testicular atrophy, it was postulated that the length of the CAG repeats of exon 1 of the AR gene was negatively correlated with sperm production [15]. Although a weak correlation was found by some investigators in men with idiopathic oligozoospermia, most studies could not demonstrate a clear correlation between the length of the CAG repeats and male infertility [29, 5]. Perhaps such a correlation only exists in a subset of infertile men in which other causes of male infertility are excluded.

Hypogonadism and male infertility

Low testosterone or increased levels of LH are present in 20–30% of male infertility cases [6]. Hypogonadism can be caused by testicular insufficiency, androgen resistance in the target organ or can be secondary to failure of the hypothalamic-pituitary endocrine system. We found hypogonadotrophic hypogonadism to be present in 3.4% of men screened for infertility [19]. Table 1 summarises the main causes of hypogonadism.

Acute and chronic disease suppresses spermatogenesis either by affecting gonadal function directly or by inhibition of GnRH and gonadotrophins. This will result in low levels of circulating and intratesticular testosterone. Also, severe undernutrition and metabolic deficiencies inhibit testicular endocrine function. Some conditions such as liver disease, hyperthyroidism and severe obesity are accompanied by increased levels of sex hormone binding globulin (SHBG) and decreased bioavailable testosterone. This reversible suppression of reproductive function during systemic disease, fever and catabolic states has been referred to as ''ontogenic regression'' [6]. Evolutionary, this temporary endocrine inhibition of reproduction may be explained to exist until more favourable circumstances are present.

In ageing males, spermatogenesis is gradually decreased by a reduction of sertoli cells and leydig cells, up to 50% after the age of 60. Testicular biopsy shows marked hypospermatogensis [17].

Table 1 Aetiology of hypogonadism (from Nieschlag and Behre 1997)

Hypothalamic-pituitary origin
Idiopathic hypogonadotrophic hypogonadism (including Kallman syndrome)
Prader-Labhart-Willi syndrome
Laurence-Moon-Biedl syndrome
Constitutional delay of puberty
Pituitary insufficiency/adenomas
Pasqualini syndrome
Hyperprolactinemia
Hemochromatosis
Testicular insufficiency
Congenital anorchia
Acquired anorchia
Klinefelter syndrome
XYY syndrome
XX male
Noonan syndrome
Gonadal dysgenesis
Leydig cell tumours
Maldescended testes
Varicocele
Sertoli-cell-only syndrome
Systemic disease, like renal failure, cirrhosis, diabetes
Male pseudohermaphroditismus due to enzyme defects in testosterone biosynthesis or LH-receptor defects
Target organ resistance to androgens
Testicular feminisation
Reifenstein syndrome
Perineoscrotal hypospadia with pseudovagina
Infertility with androgen resistance
Undervirilised fertile male syndrome

Testosterone supplementation

In the 1960s androgens were used as stimulatory or rebound therapy for idiopathic oligo/asthenozoospermia. Two different strategies were used:

- Androgens were administered in a form and dose that did not influence pituitary gonadotrophins secretion to stimulate the spermatogenesis or influence the sperm transport and maturation through an effect on the epididymis, ductus deferens and seminal vesicles.
- Androgens were used to suppress gonadotrophins and spermatogenesis with a rebound effect after stopping the therapy.

Initial results of trials concluded that androgens had little to no effect on endocrine outcomes and sperm parameters [4]. In a recent Cochrane database review [24], it was concluded that there is not enough evidence to evaluate the use of androgens for male subfertility. Randomised control trials including 930 patients were unable to show any benefit from testosterone supplementation, nor any rebound effects in men with idiopathic oligozoospermia. Also, treatment with human chorionic gonadotrophin (HCG) failed to improve male infertility. However, there may be a subset of infertile men benefiting from higher levels of testosterone by administration of gonadotrophins, for instance men with partial androgen insensitivity syndrome and men with deficient AR function [15].

Spermatogenesis and fertility can be seriously impaired or lost by chemotherapy and irradiation. Germ cells are very susceptible to cytotoxic therapy due to their high meiotic cell division rate. Also, stem cells can be irreversibly damaged by irradiation of the gonad. In rodents it has been shown that downregulating the spermatogenic process by administration of GnRH agonists or antagonists during cytotoxic treatment will result in the recovery of spermatogenesis after treatment. In humans, however, GnRH agonists were not found very effective in protecting the testis during chemotherapy [8]. This could be due to the high levels of intratesticular testosterone, despite GnRH suppression. Recently, Meistrich et al. showed in an animal model that high levels of intratesticular testosterone inhibit spermatogonial proliferation when germ cells were damaged by irradiation. Testosterone may be toxic in the irradiated testis and suppression of intratesticular testosterone during and shortly after cancer therapy may potentially stimulate recovery of spermatogenesis afterwards. Although the exact mechanism is still unknown, future hormonal trials should be performed in men who can become infertile from chemotherapy or irradiation [13].

Anabolic-androgenic steroids and infertility

Anabolic-androgenic steroids (AAS) are synthetic derivatives of testosterone. By binding the androgen receptor, they have an effect on male sexual characteristics such as secondary sexual characteristics, fertility and the anabolic status of somatic tissues.

The medical indications for anabolic steroid prescription are limited but include aplastic anaemia, severe osteoporosis and the treatment of muscle wasting in HIV or cancer patients. Physiological androgen deficiency, caused by androgen insensitivity syndrome or age-related partial androgen deficiency, is treated with testosterone rather than synthetic androgens. Androgenic steroids are still under investigation as a form of hormonal male contraception.

The most well-known use of anabolic androgenic steroids is in sports, particularly in both professional and recreational bodybuilding [23]. It is estimated that 3–12% of male athletes of high school age in the US have used steroids, while the incidence of steroid use in college athletes is 14% and 30–75% in professional athletes or bodybuilders. The doses used in power sports may be up to 40 times higher than physiological replacement doses because high doses are thought to improve muscle size and strength and therefore enhance athletic performance. Furthermore, multiple preparations are used in cycles of 4–12 weeks to maximise steroid receptor binding and increase the desired effect, followed by weeks of abstinence to prevent dependence [11].

Exogenous administration of synthetic testosterone results in negative feedback on the hypothalamic-pituitary axis and thus inhibition of the secretion of both FSH and LH. Despite normal-to-high serum androgen concentrations achieved with anabolic steroid use, those concentrations may not produce the testicular concentrations necessary to maintain spermatogenesis and many male users of anabolic steroids develop hypogonadotrophic hypogonadism with subsequent testicular atrophy and azoospermia.

Infertility following anabolic steroid abuse commonly presents as oligo- or azoospermia along with abnormalities in sperm motility and morphology. Usually, the sperm quality recovers spontaneously within 4 months after cessation of anabolic steroid abuse. However, the effect on the spermatogenesis may persist for up to 3 years in concordance with low serum testosterone and low FSH and LH levels [23].

Several case reports describe successful treatment with HCG and testosterone when semen parameters and endocrine levels are not restored within 6 months after discontinuation of AAS. Virilisation involves weekly doses of testosterone i.m. and induction of the spermatogenesis with gonadotrophins. Also, clomifencitrate, an anti-estrogen, has been applied to stimulate hypothalamic-pituitary function.

Anabolic steroid-associated male infertility is underdiagnosed, but a potentially treatable form of drug-related infertility. On account of the high percentages of abuse of AAS, it is recommended to consider this cause of azoospermia in subfertile man and regard hormonal treatment as a successful alternative if the spermatogenesis does not recover spontaneously.

Conclusions

Androgens are essential in male reproductive development and function. Testosterone, together with FSH, is needed for normal spermatogenesis. Low circulating levels of testosterone can be found in 20–30% of infertile men, but administration of testosterone or gonadotrophics does not result in improved sperm production. Testosterone, together with other hormones, can effectively block spermatogenesis and can be used as male contraceptive. Also, downregulation of intratesticular testosterone can protect fertility during cytotoxic treatment. Abuse of anabolic-androgenic steroids is a frequent cause of male infertility in recreational bodybuilders and chronic abuse of high doses of testosterone may cause hypogonadism that can last several years after discontinuation.

References

1. Bentvelsen FM, McPhaul MJ, Wilson JD, George FW (1994) The androgen receptor of the urogenital tract of the fetal rat is regulated by androgen. Mol Cell Endocrinol 105(1):21–26
2. Brinkmann AO, Jenster G, Ris-Stalpers C, van der Korput JA, Bruggenwirth HT, Boehmer AL, Trapman J (1995) Androgen receptor mutations. J Steroid Biochem Mol Biol 53(1–6):443–448

3. Cooper TG (1996) Epididymis and sperm function. Andrologia 28[Suppl 1]: 57–59
4. De Kretser DM, Burger HG, Fortune D, Hudson B, Long AR, Paulsen CA, Taft HP (1972) Hormonal, histological and chromosomal studies in adult males with testicular disorders. J Clin Endocrinol Metab 35:392–401
5. Giwercman YL, Xu C, Arver S, Pousette A, Reneland R (1998) No association between the androgen receptor gene CAG repeat and impaired sperm production in Swedish men. Clin Genet 54:435–436
6. Handelsman DJ (1994) Testicular dysfunction in systemic disease. Endocrinol Metab Clin North Am 23:839–856
7. Johnsen SG (1978) Maintenance of spermatogenesis induced by HMG treatment by means of continuous HCG treatment in hypogonadotrophic men. Acta Endocrinol 89(4):763–769
8. Kreuser ED, Klingmuller D, Thiel E (1993) The role of LHRH-analogues in protecting gonadal functions during chemotherapy and irradiation. Eur Urol 23(1):157–163
9. La Spada AR, Wilson EM, Lubahn DB, Harding AE, Fischbeck KH (1991) Androgen receptor gene mutations in X-linked spinal and bulbar muscular atrophy. Nature 4;352:77–79
10. Levalle O, Zylbersztein C, Aszpis S, Aquilano D, Terradas C, Colombani M, Aranda C, Scaglia H (1998) Recombinant human follicle-stimulating hormone administration increases testosterone production in men, possibly by a Sertoli cell-secreted nonsteroid factor. J Clin Endocrinol Metab 83(11):3973–3976
11. Lloyd FH, Powell P Murdoch AP (1996) Anabolic steroid abuse by bodybuilders and male subfertility. Br Med J 313:100–101
12. McLachlan RI, O'Donnell L, Meachem SJ, Stanton PG, de K, Pratis K, Robertson DM (2002) Hormonal regulation of spermatogenesis in primates and man: insights for development of the male hormonal contraceptive. J Androl 23(2):149–162
13. Meistrich ML, Shetty G (2003) Suppression of testosterone stimulates recovery of spermatogenesis after cancer treatment. Int J Androl 26(3):141–146
14. Nieschlag E, Behre HM (eds) (1997) Andrology: male reproductive health and dysfunction. Springer, Berlin, Heidelberg, New York
15. Ochsenkuhn R, De Kretser DM (2003) The contributions of deficient androgen action in spermatogenic disorders. Int J Androl 26(4):195–201
16. O'Donnell L, Robertson KM, Jones ME, Simpson ER (2001) Estrogen and spermatogenesis. Endocr Rev 22(3):289–318
17. Paniagua R, Nistal M, Saez FJ, Fraile B (1991) Ultrastructure of the aging human testis. J Electron Microsc Tech 19(2):241–260
18. Parker KL, Schimmer BP, Schedl A (1999) Genes essential for early events in gonadal development. Cell Mol Life Sci 55:831–838
19. Pierik FH, Van Ginneken AM, Dohle GR, Vreeburg JT, Weber RF (2002) The advantages of standardized evaluation of male infertility. Int J Androl 23(6):340–346
20. Sharpe RM, Kerr JB, McKinnell C, Millar M (1994) Temporal relationship between androgen-dependent changes in the volume of seminiferous tubule fluid, lumen size and seminiferous tubule protein secretion in rats. J Reprod Fertil 101(1):193–198
21. Singh J, O'Neill C, Handelsman DJ (1995) Induction of spermatogenesis by androgens in gonadotropin-deficient (hpg) mice. Endocrinology 136(12):5311–5321
22. Sun YT, Irby DC, Robertson DM, de Kretser DM (1989) The effects of exogenously administered testosterone on spermatogenesis in intact and hypophysectomized rats. Endocrinology 125(2):1000–1010
23. Turek PJ, Williamsl RH, Gilbaugh JH, Lipshultz LI (1995) The reversibility of anabolic steroid-induced azoospermia. J Urol 153(5):1628–1630
24. Vandekerckhove P, Lilford R, Vail A, Hughes E (2000) Androgens versus placebo or no treatment for idiopathic oligo/asthenospermia. Cochrane Database Syst Rev 2:CD000150
25. van Roijen JH, Ooms MP, Weber RF, Brinkmann AO, Grootegoed JA, Vreeburg JT (1997) Comparison of the response of rat testis and accessory sex organs to treatment with testosterone and the synthetic androgen methyltrienolone (R1881). J Androl 18(1):51–61
26. Vreeburg JT (1975) Distribution of testosterone and 5alpha-dihydrotestosterone in rat epididymis and their concentrations in efferent duct fluid. J Endocrinol 67(2):203–210
27. Walsh PC, Madden JD, Harrod MJ, Goldstein JL, MacDonald PC, Wilson JD (1974) Familial incomplete male pseudohermaphroditism, type 2. Decreased dihydrotestosterone formation in pseudovaginal perineoscrotal hypospadias. N Engl J Med 291(18):944–949
28. Weinbauer GF, Nieschlag E (1993) Gonadotrophin-releasing hormone analogue-induced manipulation of testicular function in the monkey. Hum Reprod 8[Suppl 2]: 45–50
29. Zitmann M, Nieschlag E (2003) The CAG repeat polymorphism within the androgen receptor gene and maleness. Int J Androl 26(2):76–83