FINASTERIDE AND ERECTILE DYSFUNCTION: FACT OR FICTION?

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ABSTRACT

Finasteride is a selective 5-alpha reductase isoenzymes (SRD5A2) inhibitor of the testosterone to dihydrotestosterone (DHT) conversion at the prostate and hair follicles, being used since the 90s to reduce androgenic effects in the treatment of lower urinary obstructive symptoms caused by benign prostate hyperplasia and also in androgenetic alopecia. Recent studies – with a low grade of evidence – described a percentage of 92% of erectile dysfunction after its use, raising media and medical concern. Analyzing blinded randomized placebo-controlled studies, the mean incidence of erectile dysfunction was 15% vs. 6% in the control group of finasteride 5 mg users for begin prostate hyperplasia and 4% vs. 2% in younger men taking finasteride 1 mg for androgenetic alopecia. Most cases were reversible, upon drug discontinuation or not. Erectile dysfunction prevalence increased with age, the presence of urinary obstructive symptoms and cardiovascular risk factors. Altogether, blinded finasteride use slightly increased the relative risk of erectile dysfunction, the possible mechanism underneath being a subtle interference with corpus cavernous nitric oxide generation after DHT reduction that could potentiate other causes of nitric oxide reduced bioavailability and endothelial dysfunction. However, when medical advice about sexual adverse effects was given together with finasteride prescription, the risk of erectile dysfunction was almost three times higher, creating a nocebo effect. In conclusion, erectile function and erectile dysfunction risk factors should be assessed before and during finasteride therapy; the kind of information a physician should give along with the prescription should be well based and dosed, in the sense of doing more good than harm to an individual patient.

Key words. Finasteride; erectile dysfunction; benign prostate hyperplasia; androgenetic alopecia.

FINASTERIDA E DISFUNÇÃO ERÉTIL: FATO OU FICÇÃO?

A finasterida é um inibidor seletivo da isoenzima 5-alfa redutase (SRD5A2) que converte testosterona em dihidrotestosterona na próstata e nos folículos pilosos, sendo usado desde a década de noventa para reduzir efeitos androgênicos no tratamento de sintomas e sinais de obstrução urinária por hiperplasia prostática benigna e na alopecia androgenética. Estudos recentes – com baixo grau de evidência – descreveram 92% de disfunção da ereção após seu uso, o que preocupa a mídia e o meio médico. Analisando-se estudos cegos randomizados placebo-controlados, a incidência média da disfunção foi 15% vs. 6% em controles de usuários de finasterida 5 mg para hiperplasia prostática benigna e 4% vs. 2% em homens jovens com uso de finasterida, 1 mg, para alopecia androgenética. A maioria dos casos foi reversível mediante descontinuação da droga ou não. A prevalência da disfunção aumentou com a idade, presença de manifestações de obstrução urinária e fatores de risco cardiovascular. No total, o uso cego de finasterida aumentou discretamente o risco relativo de disfunção da ereção, possivelmente por interferência sutil na produção de óxido nítrico pelo corpo cavernoso após redução de di-hidrotestosterona, que poderia potencializar outras causas de menor biodisponibilidade de óxido nítrico e disfunção endotelial. Entretanto, quando o aconselhamento médico sobre efeitos sexuais adversos foi fornecido junto à prescrição de finasterida, o risco da disfunção quase triplicou, criando um efeito nocebo. Em conclusão, deve se avaliar função de ereção e fatores de risco para disfunção antes e durante o tratamento com finasterida. O tipo de informação que o médico deve dar junto à prescrição deve ser embasado e dosado em cada indivíduo, no sentido de fazer mais bem do que mal.

Palavras-chave. Finasterida; disfunção erétil; hiperplasia prostática benigna; alopecia androgenética.
In 1991, finasteride was described as the first of 5-alpha reductase inhibitors, a class of drugs that reduce dihydrotestosterone (DHT) formation, derived from testosterone (T). At the androgen receptor, compared to T, DHT has a higher binding affinity and up to 10 x the activation capacity. Because DHT is a much more potent androgen than T, the net result of 5 alpha-reductase inhibition is a decrease in androgenic, especially proliferative, effects.

Membranes of androgen sensitive cells contain one of the two 5-alpha reductase isoenzymes, SRD5A1 and SRD5A2, originated from different genes. SRD5A1 is expressed in the liver, kidney, skin and brain. Finasteride is a selective SRD5A2 5-alpha reductase inhibitor, and this is the isoenzyme that predominates in the prostate, besides being present at lower levels in hair follicles and the liver.

Animal and clinical studies consistently showed that finasteride reduced prostate size, and soon it was approved for the treatment of lower urinary tract symptoms caused by benign prostatic hyperplasia. More recently, it was considered for prostate cancer prevention, without a clear-cut conclusion. In the PCPT (Prostate Cancer Prevention Trial), a prospective double-blind randomized study sponsored by the American Cancer Institute and the National Institute of Health (NIH), finasteride 5 mg during 7 years was shown to decrease the prevalence of prostate cancer compared to placebo in 9,060 healthy men over 55 years old by 24.8% (18.4% in men taking finasteride compared to 24.4% in the placebo group, p < 0.001). However, a higher proportion of high-grade tumors (Gleason score >7) was present in the finasteride group (6.4%) compared with controls (5.1%, p = 0.005).

In 1997, the Food and Drug Administration (FDA) approved finasteride as the first oral treatment for androgenetic alopecia in men, at an optimal dose of 1 mg. The safety profile demonstrated with previous prostate studies contributed to further employing this drug for a mostly esthetic indication.

Meanwhile, post-marketing adverse effects were assigned to finasteride considering that the T/DHT imbalance caused by its use could promote negative effects on sexual function, gynecomastia, depression, and thus impair quality of life. An experimental short term (eleven weeks) double-blind placebo-controlled study used nocturnal penile tumescence, an objective method for assessing erectile dysfunction and showed no difference after finasteride 5 mg. However, diminished libido and erectile dysfunction (that sometimes persisted upon discontinuance) were reported in a subset of finasteride users during different clinical trials, raising the possibility of a causal relationship. In the earlier studies where finasteride 5 mg was used for begin prostate hyperplasia, the mean reported incidence of sexual adverse effects was 15% (ranging from 2.1% to 38%), which is not far from the spontaneous incidence of sexual disorders over time in middle-aged and elderly men.

Our group studied 216 Brazilian men over 50 years of age spontaneously seeking for osteoporosis screening, after it was offered in Rio de Janeiro (radio, newspaper and TV). When submitted to a validated sexual function questionnaire (IIEF-5), 147 men (74% of the subjects) disclosed some grade of erectile dysfunction. The prevalence of any degree of erectile dysfunction was 48.6% in men aged 50-59 years, rising to 69.7% in those aged 60-69 years and to 83.7% of those over 70 years. The severity of erectile dysfunction was also shown to increase with age: complete erectile dysfunction was reported in 5% of men aged 40 years compared to 15% of those aged 70 years.

Erectile dysfunction was the most common of finasteride ascribed adverse sexual effects during clinical trials, followed by ejaculatory dysfunction and/or low libido. Symptoms characteristically started at the beginning of finasteride use and were partially reverted over time, with drug discontinuation or even in some patients who maintained its use. When compared to placebo, in a double-blind clinical study for begin prostate hyperplasia assembling around 600 men, any kind of sexual dysfunction was reported by 12.5% of the patients in the finasteride group compared to 4.7% in the placebo group after months. In the PROSPECT study, another placebo-controlled trial assembling 472 men with begin prostate hyperplasia, finasteride therapy was given for two years; erectile dysfunction occurred in 15.8% of the patients taking the active drug compared to 6.3% of those taking placebo (p ≤ 0.01).

Large scale placebo-controlled studies displayed similar results. In a different study design, finasteride 5 mg was maintained for 36 months while the placebo arm ceased after eleven months. At the end of three years continuously taking finasteride 5 mg, 62% of the previous sexual complaints had reverted. In the already mentioned PCPT, although the primary end-point was prostate cancer prevention, sexual dysfunction was a secondary result that was investigated in the 17,313 baseline...
participants during seven years of finasteride 5 mg or placebo. Sexual questionnaires were performed during enrollment, randomization, six months after randomization, and annually thereafter. Mean sexual dysfunction score was similar at baseline between finasteride and placebo groups and increased during the study in both, but it became higher in the group taking finasteride. At the end of 7 years the sample size was reduced to 56% of the men at study entry in the placebo arm (n = 5,169) and 52% of the men at study entry in the finasteride arm (n = 4,777), the main reason for this exit being sexual dysfunction in both groups. Treatment interval, body mass index, diabetes, hypertension, smoking, baseline vitality score at the SF-36 quality of life questionnaire, and especially older age, all had significant impacts on sexual dysfunction. Taking together the different risk factors for erectile dysfunction, the relative negative impact of finasteride on sexual dysfunction was only 0.30 and it decreased over time. Authors’ conclusion was that finasteride caused little or no sexual dysfunction for most of the healthy mean age 63 (± 5) year old men taking it for prostate cancer prevention.

Because older age was shown to be an important factor for the occurrence of sexual adverse effects after finasteride, it seemed consistent that the first clinical trials evaluating finasteride 1mg for androgenetic alopecia in usually younger populations reported a lower incidence of sexual side effects. Besides, benign prostate hyperplasia itself was associated to erectile dysfunction when LUTS were present; the reason for this association is still under debate. In fact, the mean percentage of erectile dysfunction in young men taking finasteride 1 mg for androgenetic alopecia was 4.4% compared to 2.2% of those taking placebo. A multicenter trial performed at dermatology clinics looked for short term sexual side effects of finasteride 1 mg in 186 young men with androgenetic alopecia (mean age 28.3 years, ranging from 19 to 43 years) who self-assessed their erectile function through the IIEF-5 questionnaire before and after 4 to 6 months treatment: IIEF-5 score did not change over the treatment period. Moreover, a review of clinical trials where finasteride 1 mg was used for up to 5 years revealed a small increase in sexual adverse effects, especially in the first year of use, namely: decreased libido (1.8% vs. 1.3% with placebo), erectile dysfunction (1.3% vs. 0.7% with placebo) and ejaculation disorder (1.2% vs. 0.7% with placebo), leading to a discontinuation rate of 1.2% of men due to these adverse events (compared with 0.9% of men in the placebo group). As a rule, the incidence of side-effects reported in the first year decreased over time, resolution occurred soon after drug interruption and no other adverse effect was described in these studies. A systematic review of 12 studies enclosing 3,927 patients treated with finasteride 1 mg for androgenetic alopecia confirmed that although there was an increase in the relative risk of erectile dysfunction (RR, 2.22 [95% CI, 1.03-4.78] with finasteride, the absolute risk was very low and the risk of treatment discontinuance due to sexual adverse effects was the same as placebo (RR, 0.88 [95% CI, 0.51-1.49]).

Curiously, a recent trial performed with young men taking finasteride 1 mg for androgenetic alopecia reported a much higher incidence of sexual adverse effects, reaching 94% of low libido, 92% of erectile dysfunction, 92% of decreased arousal, and 69% of problems with orgasm, thus leading to a significant decrease in sexual episodes per month and to an increase in the total sexual dysfunction score. Symptoms were reported to persist for 40 months in 20% of the patients from the time of finasteride interruption. However, this study assembled a small sample of men, not randomly selected, it was neither blind nor controlled with placebo, and, importantly, medical and midia advice along the time began to include sexual adverse effects warning, that could represent a suggestion together with the medical prescription. Nonetheless, this recent biased report raised even more midia concern – and comments – about finasteride sexual adverse effects.

An interesting Italian study reinforcing the power of suggestion through medical prescription regarding specifically finasteride was performed in 107 men with the clinical diagnosis of benign prostate hyperplasia, sexually active at baseline, i.e., with a normal erectile function score at the IIEF questionnaire. All patients received finasteride 5 mg for 1 year in a blinded way, as a compound with proven efficacy for benign prostate hyperplasia. Above that, they were randomly assigned to group 1, where sexual side effects were not mentioned upon prescription and group 2, where patients were informed that the drug could cause erectile dysfunction, decreased libido and ejaculatory problems, although the occurrence of such effects was uncommon. Sexual function questionnaires were performed at six and eleven months after prescription. In group 2 the incidence of sexual side effects was almost three times higher.
than in group 1 (43.6% vs. 15.3%, p = 0.03). The prevalence of each type of sexual disorder in group 2, compared to group 1, was proportionally higher: erectile dysfunction (30.9% vs. 9.6%, p = 0.02) was the most common, followed by decreased libido (23.6% vs. 7.7%, p = 0.04) and ejaculatory disorder (16.3% vs. 5.7%, p = 0.06). The authors concluded that a similar scenario could occur in clinical practice, and a significantly higher proportion of sexual dysfunction could be attributed to previous information on sexual side effects, by the prescribing physician or through the drug information sheet.

Having in mind that the prevalence of sexual side effects associated with finasteride use depends upon age and other risk factors for erectile dysfunction, and it may be very much amplified depending on previous medical and midia advice, still a small percentage of sexual side effects were shown to occur in blinded studies compared to placebo. What could be the mechanisms underlying these consequences?

Uygur et al. prospectively studied serum T, DHT, follicle stimulating hormone (FSH) luteinizing hormone (LH), prolactin, aldosterone, cortisol, and dehydroepiandrosterone, as well as PSA levels, uroflowmetry and sexual status through questionnaires at baseline, after 3 and 6 months in 48 patients with a mean age of 63 years, in whom 5 mg finasteride was given for symptoms of benign prostate hyperplasia. After 3 and 6 months, respectively, DHT had decreased by 60% and 75%, T increased by 15% and 26%; FSH decreased by 24% and 40% and LH also decreased by 16% and 25%, while the other hormones did not change. T, FSH, and LH levels remained within the normal range even after 6 months of finasteride but DHT was below normal reference values. PSA levels decreased by 42% and 50% at 3 and 6 months respectively; erectile dysfunction occurred in 22% of the previously potent individuals at 3 months and in 33% by 6 months. Gynecomastia appeared in 4% of the patients by the sixth month. Unfortunately, estradiol and SHBG levels were not measured nor sexual adverse effects correlated with serum hormone levels. Besides, plasma gonadotropins dosage was performed by a single measure at 8.am, a questionable strategy for assessing pulsatile hormone levels. At the lower 1 mg dosage, used for androgenic alopecia, finasteride also decreased DHT levels by 71%, after 42 days of treatment, but serum LH and FSH did not change.

However, it remains to be proved if the serum hormonal changes caused by finasteride have a direct impact on sexual function. It doesn’t seem so in the model of T and DHT physiological actions available from the 5-alpha reductase-2 deficiency syndrome. Affected individuals are 46,XY subjects with complete or incomplete SRD5A2 congenital deficiency leading to various degrees of ambiguous external genitalia, from a clitoral-like fallus to penile hypospadia, and additionally a frequent incidence of scrotal, inguinal or abdominal cryptorchidism. Characteristically, as a function of T action, internal genitalia enclosing seminal vesicles, vasa deferentia, epididymides and ejaculatory ducts are normal. Because DHT is important for its development, the prostate of these individuals is small, often rudimentary. Upon puberty, T actions were shown to occur normally: there is an increase in muscle mass, deepening of the voice, testicle, scrotal and fallus enlargement. Final height and libido are not impaired in these subjects. However, facial and body hair are decreased due to DHT low levels and baldness has never been observed in these men. Sexual function is reported as normal and sleep-related erections were documented to happen regularly, through penile tumescence recording in young affected individuals. Biochemical features in this syndrome are the same as the reported with finasteride use, except that FSH levels may be above the reference range in the cases of cryptorchidism. Sperm concentrations depended if testes descended or not; nonetheless some patients had been reported to father children.

Evidence has been extensively presented that testosterone is the sexual hormone linked with libido, with a subtle influence on erectile function, which is mostly dependent on vascular integrity. Testosterone levels are increased during finasteride use, leaving little elements to attribute low sexual desire and erectile dysfunction as a direct consequence of hormonal imbalance. Most authors agree that DHT is less important than T in erectile function and that 5-alpha reductase inhibitors do not cause erectile dysfunction to a significant degree. The hypothesis that the human brain could be a mediator of T effects on libido and erectile function through its transformation to DHT is weakened by the fact that the 5-alpha reductase isoenzyme present in the brain is SRD5A1, and this is not the one that finasteride inhibits.

Local vascular factors may play a role in finasteride associated erectile dysfunction, as androgen receptors have been identified in the cavernous tissue. A proposed mechanism for 5-alpha reductase
inhibition-related erectile dysfunction is the reduction of nitric oxide synthase activity in the penis by decreasing neuronal and endothelial nitric oxide synthase transcription, as was demonstrated with high finasteride doses.27 Probably this is a parallel mechanism from the well described endothelial dysfunction caused by hypertension, diabetes or pre-diabetic states, previously undiagnosed dyslipidemia, all these being conditions in which erectile dysfunction can be an early marker for cardiovascular disease, that can be present decades before any coronary artery event. However, one condition could potentiate another. Finasteride could precipitate erectile dysfunction in men with already subtle endothelial dysfunction due to mild cardiovascular risk factors, as opposed to young and otherwise healthy 5-alpha reductase-2 deficiency syndrome patients, who were not shown to present erectile dysfunction. This hypothesis has yet to be tested.

In conclusion, erectile dysfunction prevalence increases with age, in the presence of lower urinary tract symptoms from begin prostate hyperplasia and cardiovascular risk factors that impair nitric oxide bioavailability. Finasteride was associated with a very small percentage of sexual side effects in randomized blinded studies compared to placebo, mainly in the first year and revertible upon drug discontinuance or even without interrupting the drug. Sexual side effects, especially erectile dysfunction, have been hugely amplified through medical and midia advice, creating a nocebo effect.

One point seems crucial: to objectively evaluate sexual function before and during finasteride therapy and to look for risk factors for erectile dysfunction, especially in older patients and in those who present begin prostate hyperplasia. A good instrument for erectile dysfunction diagnosis and follow-up is the IIEF-5 questionnaire, developed by Rosen et al.28 and validated in Brazil by Rhoden et al.29 The IIEF-5 has a maximum score of 25; scores above 21 are considered normal, without erectile dysfunction. Lower scores indicate erectile dysfunction of increasing severity: mild erectile dysfunction (17 to 21), mild to moderate erectile dysfunction (12 to 16), moderate erectile dysfunction (8 to 11), and severe erectile dysfunction (5 to 7). Using a cut-off of < 22 points, the IIEF-5 demonstrated a sensitivity of 98% and a specificity of 88% for the detection of the presence and severity of erectile dysfunction.

The kind of information a physician should give along with finasteride prescription remains controversial. Some authors defend a full description of reported sexual side effects, whereas others argue that this procedure could increase the probability of erectile dysfunction, by the power of suggestion. The way information is given, patient’s background, further questioning about sexual function during the follow-up, all these factors have to be well based and dosed otherwise they could result in a higher percentage of nocebo sexual adverse effects. The “do no harm” principle has to be thought also for the words a physician addresses his patients.

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REFERENCES


ABSTRACT

**Finasteride for benign prostatic hyperplasia**

Benign prostatic hyperplasia, a non-malignant enlargement of the prostate in aging men, can cause bothersome urinary symptoms (intermittency, weak stream, straining, urgency, frequency, incomplete emptying).

Drug-related adverse effects for finasteride are rare; nevertheless, men taking finasteride are at increased risk for impotence, erection dysfunction, decreased libido and ejaculation disorder, versus placebo. Versus doxazosin, which has higher rates of dizziness, postural hypotension, and asthenia, men taking finasteride are at increased risk for impotence, erection dysfunction, decreased libido, and ejaculation disorder. Finasteride significantly reduces asthenia, postural hypotension, and dizziness versus terazosin. Finasteride significantly lowers the risk of asthenia, dizziness, ejaculation disorder, and postural hypotension, versus finasteride + terazosin.