SEXUAL MEDICINE REVIEWS REVIEW

# Sexual Problems of Men With Androgenic Alopecia Treated With 5-Alpha Reductase Inhibitors

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ABSTRACT

**Introduction:** 5-Alpha reductase inhibitors (5-ARIs) are widely used in the treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia (AGA).

**Aim:** To examine all available data on the effects of 5-ARIs on sexual functioning in AGA treatment and to assess whether 5-ARIs increase the risk of sexual dysfunction.

**Methods:** A literature review of publications at PubMed related to the subject was used.

**Main Outcome Measure:** We assessed erectile dysfunction, ejaculation impairment, and decreased libido.

**Results:** 5-ARIs may cause side effects such as erectile dysfunction, ejaculation problems, and decreased libido in patients. Their long-term impact and precise mechanism have not been clarified. Data from studies on 5-ARIs are important for drug selection and patient counseling. More training and awareness is needed for clinicians and patients to recover many patients from sexual adverse effects.

**Conclusion:** 5-ARIs used in the treatment of AGA have well-defined side effects, which can negatively affect sexual life. It is unknown and unpredictable which men using these drugs may be subject to these side effects and when these effects may appear. Studies have been insufficient to provide a clear answer to this question. **Coskuner ER, Ozkan B, Culha MG. Sexual Problems of Men With Androgenic Alopecia Treated With 5-Alpha Reductase Inhibitors. Sex Med Rev 2018;XX:XX–XX.**



**Key Words:** Finasteride; Dutasteride; 5-Alpha Reductase Inhibitor; Androgenic Alopecia; Sexual Dysfunction

## INTRODUCTION

5-Alpha reductase inhibitors (5-ARIs) are a class of anti-androgenic drugs. They are widely used in the medical treatment of benign prostatic hyperplasia (BPH) and androgenic alopecia (AGA; male pattern hair loss). Currently, 2 types of 5-ARIs, dutasteride and finasteride, are used in clinical practice. Clinical effects are based on their ability to inhibit the 5-alpha reductase enzyme responsible for the conversion of testosterone to its active derivative, dihydrotestosterone (DHT).[1]

In recent years, there has been increasing concern about the possibility of adverse effects on sexual function from these medications, including persistent erectile dysfunction (ED), loss of libido, decreased volume of ejaculate, and depression. Sexual side effects have been reported in about 2% of people who had clinical trials with 1-mg finasteride for AGA.[2] It is thought that the adverse side effects of 5-ARIs are clinically less important in these sexual side effects. However, in some patients, these sexual side effects are persistent or irreversible, with accompanying negative emotional transition and decreased quality of life.[3,4]

The effects of 5-ARIs on sexual function are important to investigate. Various systematic reviews published since 2002 assessed the effectiveness and reliability of 5-ARIs.[5–7] 2 Meta-analyses found that using finasteride for AGA treatment was safe and that the drug-related adverse effects were rare.[5,6] However, the quality of safety reporting has not been assessed. The fact that the adequacy and generalizability of blinding was not assessed in a recent meta-analysis has seriously limited the quality of these clinical trials.[8] Published reports of clinical trials have provided insufficient information to create a safety profile. The aim of this review is to assess the sexual problems of patients using 5-ARIs because of AGA.

## METHODS

The literature on sexual problems with the use of 5-ARIs was reviewed via a PubMed search for articles published between 1990-December 2017 using the following combination of key

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words: "5-ARI's-finasteride," "dutesteride," "androgenic alopecia," and "sexual dysfunction." All articles were screened based on titles and abstracts. The final selection was made after reading the full texts of these articles. Reference lists from selected articles were searched manually for additional relevant references.

## Definition and Pathophysiology of AGA

AGA is the most common cause of progressive hair loss in men and is caused by the interaction of endocrine factors and genetic predisposition. Approximately 30−50% of men aged 50 years are affected by AGA, and the rate is 80% at age 80 years.[9] AGA can also rarely begin with puberty and increase with age.[10] Psychological pressure, anxiety, and depression can occur in men affected by this situation; such men consider themselves old and less attractive, and their social life may be restricted over time.[11]

Androgens, testosterone, and DHT are the main hormones in male pattern hair loss, and the fact that some hair follicles are resistant to androgens explains why there is no hair loss in every man. Considering that hair follicles on the sides and back of the head are resistant to androgens, there is no hair loss in these areas even in the case of AGA. For men who do not have hair loss, the hair follicles at the top also are resistant to androgens. In the pathophysiology of AGA, the interaction of epithelial cells of the genetically sensitive hair follicles in androgen-dependent regions with androgens is thought to play a role.[12]

Androgens have an effect on skin physiology and pathophysiology, as well as sexual functions. Skin cells can synthesize most active androgens from gonadal or adrenal precursors. The roles of androgens and androgen receptors (ARs) in skin pathologies have long been studied, but their molecular mechanisms have not been fully elucidated. The relationship between type 2 5-alpha reductase, AR coactivators, paracrine factors in dermal papillae (transforming growth factor beta, insulin-like growth factor 1, Wnt signals, and Dickkopf-related protein 1), enzymes involved in skin steroidogenesis, and AR and Wnt signals can play a role in better understanding of the molecular mechanism and the development of new treatment options.[13]

Currently, 2 drugs—minoxidil and finasteride—approved by the Food and Drug Administration (FDA) are frequently used in the treatment of AGA.[14] Finasteride was the first 5-ARI clinically approved drug for the treatment of BPH and AGA.[1] Finasteride exerts its clinical effect by blocking the type 2 isoform of the 5-alpha reductase enzyme that converts testosterone to a more potent form of testosterone, DHT. Type 2 isoform is the predominant form especially in human prostate and hair follicles.[1] A second 5-alpha reductase enzyme inhibitor other than finasteride—dutasteride—is also used in the treatment of BPH and AGA.[3]

Finasteride is a potent and selective type 2 5-ARI and has no antiandrogen effect. 5-alpha reductase converts testosterone to DHT. DHT, which binds to hair follicles in the hairy scalp, can then cause AGA. Daily 1-mg finasteride reduces DHT in the hairy scalp by 64% and DHT in serum by 68%. Although its side effects—ED, low libido, and anorgasmia—are usually less common, they are often improved by the cessation of treatment. Although permanent sexual side effects have been mentioned in some social media and Internet forums, the actual incidence is unknown. Dutasteride has been shown to inhibit both type 1 and type 2 5-alpha reductase isoforms and to improve hair growth in younger men more than finasteride. However, sexual side effects owing to dutasteride can be seen more than with finasteride.[15]

Finasteride is preferred in high doses (5 mg) in BPH and low doses (1 mg) in AGA. The effect of finasteride on 5-alpha reductase types 2 and 3 is greater than that on type 1.[8,16] Finasteride exerts its effect on prostate, muscle, liver, kidney, brain, mammary gland, frontal cortex, skin, epidermis, pancreas, spleen, heart, stomach, dermis, small intestine, and adipose tissue.[16]

## Side Effects of 5-ARIs

Sexuality is an important parameter both in relations between couples and in terms of life satisfaction. 5-ARIs used in the treatment of AGA and BPH may have adverse effects on both erection and ejaculation.[17] According to the PLESS study, sexual side effects such as ED, loss of libido, and ejaculation impairment were reported at a rate of a maximum of 15% after 1 year of finasteride treatment.[18] In the case of low-dose (1-mg) finasteride use for AGA, there were no abnormal scores in 186 young men (aged 19−43 years, with a mean age of 28.3 years) according to the sexual health research inquiry form.[19] However, compared with the situation in clinical practice, these data are thought to be far from reality.

In patients who are knowledgeable about the side effects of the drug, experiencing a higher rate of side effects is associated with the nocebo effect.[20] Clearly, the sexual side effects observed based on the Male Sexual Function 4-item questionnaire in the blind arm of this study seem to be consistent with the 1-year outcomes of the treatment arm in randomized double-blind studies such as the PLESS study. The high incidence of the 1-year cumulative sexual side effect rate of 29.9% in all patients may play a role in the more reliable prediction of the burden of sexual side effects in clinical practice based on studies. As mentioned earlier, the maximum incidence of side effects can be seen even 1 year after treatment.[18]

Irwig and Kolukula[3] conducted a standardized interview with 71 men (healthy in terms of other aspects) aged 21−46 years in a study that they conducted to determine the duration and type of persistent sexual side effects of finasteride. Patients in their sample used finasteride temporarily, and side effects continued for at least 3 months even though the drug was discontinued. According to the distribution of sexual problems seen in those with new-onset permanent sexual dysfunction, it was found that 94% lost libido, 92% had ED, 92% had low stimulation, and 69% had orgasm problems.[3] The average duration of finasteride

use in this group was 28 months, and the average duration of permanent sexual side effects was 40 months, which was from the cessation of medication to the interview. In the participants, the mean number of sexual episodes during the month decreased, and the total sexual dysfunction score was found to be significantly higher on the Arizona Sexual Experience Scale than that determined before the use of finasteride ($P < .001$). Studies on AGA have shown that sexual side effects are improved over time or by the cessation of drug administration.[2] According to 2 pharmaceutical-funded trials by Merck, in a 1-year study of 1,553 men, the use of 1-mg finasteride daily resulted in a higher rate of sexual side effects compared with placebo (4.2% vs 2.2%, respectively; $P < .05$).[2] In the same study, loss of libido (1.9% vs 1.3%), decrease in ejaculate volume (1.0% vs 0.4%), and ED (1.4% vs 0.9%) were also found, respectively.[2] A total of 1,879 men were randomized to 1-mg finasteride or placebo for 1 year in a study conducted by Merck, where the rate of sexual side effects in the finasteride group was also found to be significantly higher (3.8% vs 2.1%, respectively; $P = .04$).[21]

In another study, 416 participants took either 5-mg finasteride or dutasteride (a dual 5-ARI) in doses of 0.05−2.5 mg for 24 weeks. Libido and ejaculation problems were more common in patients using these drugs compared with placebo, whereas there was no difference in terms of ED compared with the placebo group.[22] Phosphodiesterase type 5 inhibitors, testosterone, human chorionic gonadotropin, and clomiphene citrate are generally preferred in the medical treatment of sexual dysfunction in these patients.[3]

Basaria et al[23] compared men who used finasteride for hair loss and had persistent sexual dysfunction after drug withdrawal with men who used finasteride but did not have any symptoms and with men who never used any medication. A recent study reported that men with post finasteride syndrome may experience symptoms such as decreased penile sensation, decreased ejaculatory force, low penile temperature, decreased ejaculatory volume, anhedonia, loss of mental concentration, and decreased muscle tonus and mass.[24] In another immunohistochemical study, an increase in AR levels was found in epithelial and stromal cells of foreskin in 8 men with post finasteride syndrome compared with healthy men.[25]

Both types of 5-ARIs are used by younger patients.[26] Finastertide is frequently used by young men and is indicated for the prevention and reversal of male pattern baldness. In a study of 1,553 young men (18−41 years of age), 1.4% of those using finasteride had ED, whereas only 0.9% of men exposed to placebo had ED.[2]

## DISCUSSION

The conversion of testosterone to DHT plays a key role in normal sexual function, whereas progesterone and its metabolites are other possible actors. 5-alpha reductase not only converts testosterone to DHT but also reduces glucocorticoids and progestins irreversibly. In both humans and mice, the progesterone affinity of 5-alpha reductase as a substrate is greater than that of testosterone and androstenedione.[27] Progesterone is synthesized locally de novo or from circulating precursors in the brain and provides myelinization of the central nervous system. Progesterone and its metabolites also modulate various neurotransmitter receptors such as $GABA_A$, sigma-1, and nicotinic acetylcholine. Metabolites transformed by 5-alpha reductase are transformed into other metabolites by 3 alpha-hydroxysteroid dehydrogenase.[28] There is also a significant association between DHT inhibition and erection.[29] In a study conducted on castrated rats, testosterone replacement has been shown to lead to more erections by electrical stimulation in rats compared with those that received testosterone and 5-ARIs.[30] It is also known that DHT treatment improves the nocturnal penile tumescence in elderly men with low testosterone levels.[31] DHT was also more successful in maintaining erection than placebo in patients with symptoms of andropause and serum total testosterone levels <15 nmol/L.[32]

The relationship between finasteride and transient sexual dysfunction has been demonstrated by randomized controlled trials. Owing to the effects of androgens and progestins on libido, orgasm, and erectile function in the brain and peripheral nervous system, finasteride may also be held responsible for persistent side effects. Other studies are necessary to determine the true incidence of permanent sexual side effects, determine who is more susceptible to this effect, and clarify the underlying mechanism. However, when using finasteride in the treatment of AGA, it is necessary for doctors to warn patients about potential permanent sexual side effects.

Basaria et al[23] showed that persistent sexual dysfunction after drug withdrawal in men who used finasteride. Because the symptoms in these patients are similar to those found in the androgen insufficiency, those authors sought answers to which of the following the permanent symptoms depend: permanent suppression of the hypothalamic-hypophyseal-testicular axis by finasteride, irreversible suppression of 5-alpha reductase, off-target suppression of the AR activity, or impairment of regions of the brain that regulate sexual function or mood. Group 1 consisted of men who had persistent symptoms after finasteride was discontinued, group 2 consisted of age-compatible men who used finasteride but did not develop symptoms, and group 3 consisted of healthy men who did not use finasteride.[23] Among the 3 groups, there was no difference in body composition and endurance, and in nucleotide sequences of AR and 5-alpha reductase type 2 genes. In the symptomatic finasteride users, there was no difference in cognitive functions among the groups on objective assessments, although there were insufficient sexual function, high depression scores, more negative emotional balance, and more cognitive complaints.[23] Moreover, no difference was found among the 3 groups in terms of testosterone, DHT, 5 alpha-androstane-3 alpha, 17 beta-diol glucuronide, ratio of testosterone to DHT, ratio of androsterone glucuronide to

etiocholanolone glucuronide, peripheral androgenic effect, and level of AR-dependent genes expressed in the skin. They detected abnormal function in erotic and non-erotic stimulus-related brain circulatory oxygen levels by using functional magnetic resonance imaging. They found that the findings of abnormal function that could be detected were compatible with that of major depression with sexual stimulation. The authors did not find evidence of androgen insufficiency, low peripheral androgen activity, or persistent peripheral inhibition of 5-alpha reductase in patients with persistent sexual symptoms after use of finasteride.[23]

It is not clear why only a group of finasteride users experience persistent sexual symptoms and low mental sensation. There is no evidence of changes in AR, 5-alpha reductase type 1 and type 2 gene sequence changes, or changes in AR-dependent gene expression in the skin, but the possibility of involvement of other gene variants, gene expression levels in other tissues, or specific regions of the brain related to mental status and sexual functions cannot be excluded. The presence of epigenetic effects of finasteride seems likely in terms of persistent symptoms. The fact that symptomatic finasteride users do not benefit from testosterone, DHT, or any other androgen depends on the absence of androgen insufficiency, permanent 5-alpha reductase inhibition, or androgen insensitivity in these patients. Treatment should focus on depression and sexual symptoms. Moreover, men seeking treatment for AGA are known to have a higher prevalence of depression and sexual dysfunction than the general population.[33]

There are debates about why side effects of finasteride are seen in some people and not in others. In addition, there are studies that investigate possible causes of this effect. Even though a clear conclusion cannot be drawn about this subject today, studies on probable causes continue.

The amino acid protein sequence and expression level of ARs are influenced by polymorphisms in the gene. The most frequently studied polymorphisms of AR are 2 nucleotide sequences: (CAG)n and (GGN)n.[34] Long (CAG)n repeats have been shown to be associated with male infertility, whereas short (CAG)n repeats have been associated with prostate cancer in Asian and Caucasian races.[35,36] In a molecular study comparing the role of (CAG)n and (GGN)n polymorphisms in the AR gene of 69 men with AGA and post finasteride syndrome, 91 men with untreated AGA, and 78 fully healthy men on the long-term toxic effects of finasteride, it has been determined that long repeats may produce genetic predisposition for the development of AGA.[37] In their molecular study of 66 men with post finasteride syndrome, Cauci et al[38] found that there was a difference in symptoms based on the number of (CAG)n and (GGN)n repeats. AR is a member of the steroid hormone receptor superfamily and regulates the functions of androgens.[39] However, there are very few studies investigating the relationship between male sexual functions and (CAG)n repeats. Tirabassi et al[40] found that the number of AR (CAG)n triplets was negatively correlated to erectile function, sexual desire, relationship satisfaction, and International Index of Erectile Function score in their study investigating the effect of testosterone replacement therapy in men with hypogonadism on sexual function recovery. Cauci et al[38] found that short (CAG)n repeats in men with post finasteride syndrome were associated with a further decrease in sexual desire and libido, and long repeats with worse satisfaction with orgasm. Scrotal discomfort was higher in those with short (CAG)n repeats, whereas involuntary muscle spasms were higher in those with long (CAG)n repeats.[38] However, further studies are needed to show that finasteride develops faster sexual toxic effects in men with short (CAG)n repeats. Long (GGN)n repeats in men with post finasteride syndrome are associated with better status in terms of physical condition, vitality, and depressive mood. Loss of scrotal sensation and scrotal discomfort are less frequent in those with long (GGN)n repeats, but the onset of symptoms may be more frequent after finasteride is discontinued.[38] According to that study, sexual desire and loss of libido were more frequent among men with short (CAG)n repeats, whereas no difference could be found between (CAG)n and (GGN)n repeats in terms of penile discomfort, loss of scrotal sensation, scrotal discomfort, decrease in growth of pubic hair, decrease in sensory perineal fullness, involuntary muscle spasms, weight gain, dryness of skin, and onset of symptoms after use of finasteride.

## CONCLUSION

AGA is a common situation that men are interested and seeking solutions. 5-ARIs—some of the FDA-approved medicines—have been increasingly used in this context in the treatment of AGA. However, 5-ARIs have well-defined side effects that can negatively affect sexual life. The real problem is that it is unknown and unpredictable as to which men using these drugs may be subject to these side effects and when these effects may appear. Studies have been insufficient to give a clear answer to this question. More genetic and clinical studies are needed to understand the pathophysiological pathways leading to the onset and continuation of side effects in men who have used finasteride.

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## REFERENCES


1. Finn DA, Beadles-Bohling AS, Beckley EH, et al. A new look at the 5alpha-reductase inhibitor finasteride. **CNS Drug Rev 2006;12:53-76.**
2. Kaufman KD, Olsen EA, Whiting D, et al. Finasteride in the treatment of men with androgenetic alopecia. Finasteride Male Pattern Hair Loss Study Group. **J Am Acad Dermatol 1998; 39:578-589.**
3. Irwig MS, Kolukula S. Persistent sexual side effects of finasteride for male pattern hair loss. **J Sex Med 2011;8:1747-1753.**
4. Irwig MS. Persistent sexual side effects of finasteride: Could they be permanent? **J Sex Med 2012;9:2927-2932.**
5. Mella JM, Perret MC, Manzotti M, et al. Efficacy and safety of finasteride therapy for androgenetic alopecia: A systematic review. **Arch Dermatol 2010;146:1141-1150.**
6. Gupta AK, Charrette A. The efficacy and safety of 5alpha-reductase inhibitors in androgenetic alopecia: A network meta-analysis and benefit-risk assessment of finasteride and dutasteride. **J Dermatol Treat 2014;25:156-161.**
7. Tacklind J, Fink HA, Macdonald R, et al. Finasteride for benign prostatic hyperplasia. **Cochrane Database Syst Rev 2010:CD006015.**
8. Belknap SM, Aslam I, Kiguradze T, et al. Adverse event reporting in clinical trials of finasteride for androgenic alopecia: A meta-analysis. **JAMA Dermatol 2015;151:600-606.**
9. Varothai S, Bergfeld WF. Androgenetic alopecia: An evidence-based treatment update. **Am J Clin Dermatol 2014;15:217-230.**
10. Tsuboi R, Itami S, Inui S, et al. Guidelines for the management of androgenetic alopecia (2010). **J Dermatol 2012;39:113-120.**
11. Lee HJ, Ha SJ, Kim D, et al. Perception of men with androgenetic alopecia by women and nonbalding men in Korea: How the nonbald regard the bald. **Int J Dermatol 2002;41:867-869.**
12. Kwack MH, Sung YK, Chung EJ, et al. Dihydrotestosterone-inducible Dickkopf 1 from balding dermal papilla cells causes apoptosis in follicular keratinocytes. **J Invest Dermatol 2008; 128:262-269.**
13. Ceruti JM, Leiros GJ, Balana ME. Androgens and androgen receptor action in skin and hair follicles. **Mol Cell Endocrinol 2018;465:122-133.**
14. Adil A, Godwin M. The effectiveness of treatments for androgenetic alopecia: A systematic review and meta-analysis. **J Am Acad Dermatol 2017;77:136-141.e5.**
15. Traish AM. Negative impact of testosterone deficiency and 5alpha-reductase inhibitors therapy on metabolic and sexual function in men. **Adv Exp Med Biol 2017;1043:473-526.**
16. Fouad Mansour M, Pelletier M, Tchernof A. Characterization of 5alpha-reductase activity and isoenzymes in human abdominal adipose tissues. **Journal Steroid Biochem Mol Biol 2016; 161:45-53.**
17. Giuliano F. Impact of medical treatments for benign prostatic hyperplasia on sexual function. **BJU Int 2006;97(Suppl. 2):34-38 [discussion: 44-45].**
18. Wessells H, Roy J, Bannow J, et al. Incidence and severity of sexual adverse experiences in finasteride and placebo-treated men with benign prostatic hyperplasia. **Urology 2003;61:579-584.**
19. Tosti A, Pazzaglia M, Soli M, et al. Evaluation of sexual function with an international index of erectile function in subjects taking finasteride for androgenetic alopecia. **Arch Dermatol 2004;140:857-858.**
20. Hahn RA. The nocebo phenomenon: Concept, evidence, and implications for public health. **Prev Med 1997;26:607-611.**
21. Gormley GJ, Stoner E, Bruskewitz RC, et al. The effect of finasteride in men with benign prostatic hyperplasia. The Finasteride Study Group. **N Engl J Med 1992;327:1185-1191.**
22. Olsen EA, Hordinsky M, Whiting D, et al. The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: Results of a randomized placebo-controlled study of dutasteride versus finasteride. **J Am Acad Dermatol 2006;55:1014-1023.**
23. Basaria S, Jasuja R, Huang G, et al. Characteristics of men who report persistent sexual symptoms after finasteride use for hair loss. **J Clin Endocrinol Metab 2016;101:4669-4680.**
24. Chiriaco G, Cauci S, Mazzon G, et al. An observational retrospective evaluation of 79 young men with long-term adverse effects after use of finasteride against androgenetic alopecia. **Andrology 2016;4:245-250.**
25. Di Loreto C, La Marra F, Mazzon G, et al. Immunohistochemical evaluation of androgen receptor and nerve structure density in human prepuce from patients with persistent sexual side effects after finasteride use for androgenetic alopecia. **PLoS One 2014;9:e100237.**
26. Nguyen HMT, Gabrielson AT, Hellstrom WJG. Erectile dysfunction in young men—A review of the prevalence and risk factors. **Sex Med Rev 2017;5:508-520.**
27. Andersson S, Russell DW. Structural and biochemical properties of cloned and expressed human and rat steroid 5 alpha-reductases. **Proc Natl Acad Sci U St A 1990; 87:3640-3644.**
28. Stein DG. Progesterone exerts neuroprotective effects after brain injury. **Brain Res Rev 2008;57:386-397.**
29. Canguven O, Burnett AL. The effect of 5 alpha-reductase inhibitors on erectile function. **J Androl 2008;29:514-523.**

30. Seo SI, Kim SW, Paick JS. The effects of androgen on penile reflex, erectile response to electrical stimulation and penile NOS activity in the rat. **Asian J Androl 1999;1:169-174.**

31. Foresta C, Caretta N, Garolla A, et al. Erectile function in elderly: Role of androgens. **J Endocrinol Invest 2003; 26:77-81.**

32. Kunelius P, Lukkarinen O, Hannuksela ML, et al. The effects of transdermal dihydrotestosterone in the aging male: A prospective, randomized, double blind study. **J Clin Endocrinol Metab 2002;87:1467-1472.**

33. Cash TF. The psychosocial consequences of androgenetic alopecia: A review of the research literature. **Br J Dermatol 1999;141:398-405.**

34. Gottlieb B, Beitel LK, Nadarajah A, et al. The androgen receptor gene mutations database: 2012 update. **Hum Mutat 2012;33:887-894.**

35. Pan B, Li R, Chen Y, et al. Genetic association between androgen receptor gene CAG repeat length polymorphism and male infertility: A meta-analysis. **Medicine 2016;95:e2878.**

36. Sun JH, Lee SA. Association between CAG repeat polymorphisms and the risk of prostate cancer: A meta-analysis by race, study design and the number of (CAG)n repeat polymorphisms. **Int J Mol Med 2013;32:1195-1203.**

37. Cecchin E, De Mattia E, Mazzon G, et al. A pharmacogenetic survey of androgen receptor (CAG)n and (GGN)n polymorphisms in patients experiencing long term side effects after finasteride discontinuation. **Int J Biol Markers 2014; 29:e310-e316.**

38. Cauci S, Chiriaco G, Cecchin E, et al. Androgen receptor (AR) gene (CAG)n and (GGN)n length polymorphisms and symptoms in young males with long-lasting adverse effects after finasteride use against androgenic alopecia. **Sex Med 2017; 5:e61-71.**

39. Simental JA, Sar M, Lane MV, et al. Transcriptional activation and nuclear targeting signals of the human androgen receptor. **J Biol Chem 1991;266:510-518.**

40. Tirabassi G, Corona G, Biagioli A, et al. Influence of androgen receptor CAG polymorphism on sexual function recovery after testosterone therapy in late-onset hypogonadism. **J Sex Med 2015;12:381-388.**