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Original Article

The Effect of Finasteride on the Secretion of Testosterone, DHT, LH, FSH and Tissue Factors in the Testis of NMRI Mice

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Abstract

Introduction: The aim of this study was to investigate the effect of finasteride on spermatogenesis and male fertility. To do so, the effects of finasteride were examined for hormonal assays and testicular tissue changes.

Materials and Methods: This study was performed on male NMRI mice in five groups, namely control, sham, and three experimental groups that received finasteride (1, 5, and 20 mg/kg BW) for 35 days.

Results: As for hormonal observations, significant reductions of DHT in all injectable doses were recorded. Yet, testosterone only increased significantly in two doses of 5 and 20 mg/kg BW. Moreover, two hormones of FSH and LH were significantly reduced in the drug-receiving groups. In the view of histological findings, sperm count and motility were markedly different between the doses of 5 and 20 mg/kg BW in the epididymis. The frequency of primary spermatocytes, spermatids, and spermatozoids was considerably decreased in groups receiving finasteride at doses of 5 and 20 mg/kg BW. However, this happened only at a dose of 20 mg/kg BW for spermatogonial cells.

Conclusions: It is predicted that finasteride at a dose of 5 mg/kg BW and more can have side effects on male reproductive ability and spermatogenesis.

Keywords: Finasteride ; Spermatogenesis; Hormone; Tissue; Testis

1. Introduction

Spermatogenesis is the process by which diploid cells are formed by the spermatogonia of haploid sperm cells in the testicular seminiferous tubules. This process has several steps in which different cells such as spermatocytes, spermatids, and finally sperm that can move and fertilize are seen [1].

This process requires the secretion of a group of interdependent sex hormones, the most important of which is the hypothalamic-pituitary-gonadal hormone cycle, in which gonadotropin secreted by the hypothalamus causes the secretion of LH and FSH. Also, these sex hormones have a great ability to be converted to another type due to their steroid structure. One of these hormones is DHT, which is produced by the enzyme 5 alpha-reductase from testosterone. This process occurs in both sexual organs such as prostate testis and asexual organs such as the skin, causing unwanted side effects like BPH or benign prostate enlargement and androgenic hair loss in men [2].

To lower these side effects, a drug called finasteride has recently been introduced to the market. Previously prescribed to treat BPH, this drug falls in the category of azo steroids and is taken orally (5 mg/d for BPH and 1 mg/d for androgenic hair loss). The FDA-recognized drug has approved side effects such as decreased libido, depression and aggression, erectile dysfunction, and decreased semen. The mechanism of this drug is based on the competitive inhibition of the 5-alpha reductase enzyme, which is directly responsible for conversion of T to DHT and preventing conversion of serum T to DHT [3].

In 2007, research showed that men who had been taking finasteride for more than 50 weeks would experience up to 12% loss of motility and reduced sperm count [4]. In 2011, Tu et al. reported that three months of finasteride use would damage sperm DNA in men, with a direct relationship with the quantity and timing of finasteride consumption [5]. Three years later, Kang et al. found that 5 alpha-reductase enzymes play a decisive role in fertility due to sperm motility and their capacity [6]. In 2017, Fertik reported on the possibility of any side effects of 5-alpha reductase inhibitors persisting after discontinuation. These complications included decreased libido and sperm count [7].

Building on such findings, the authors of this article examined the effects of four important genes (Dazl, Tsga10, Sycp3, Prm2) on spermatogenesis to delve into the effects of finasteride on spermatogenesis. The decreased expression of these four molecular markers of spermatogenesis indicated negative effects of finasteride on spermatogenesis [8].

Finasteride is important in terms of fertility and reproduction because it is the second most widely used drug in the world to prevent androgenic hair loss, and a hefty percentage of the population consuming it are at reproductive age. Therefore, studying the side effects of this drug seems important. The present study was set to evaluate the effect of this drug on spermatogenesis and male fertility, possible tissue changes in the testicles, and possible changes in serum sex hormones in mice.
This study was conducted in conjunction with molecular research on the effects of finasteride. There is a lot of disagreement about the effect of this drug on spermatogenesis and consequently male fertility. Some confirm the negative effect of this drug on spermatogenesis and some others claim that finasteride does not have a significant effect on sperm quality and quantity. The novelty of this study is that the effect of this drug for 35 days which is a complete cycle of mouse spermatogenesis was investigated for the first time. Along with examining the histological effects of the testis, the movement and number of

sperms in the epididymis and hormonal changes have been studied.

2. Materials and Methods

This study was carried out on 60 male NMRI mice for 35 days. The mice were divided into five groups; control, sham, and three experimental groups that received finasteride (SOHA, IRAN) (1, 5, and 20 mg/kg BW) [9].

1 mg/d finasteride is prescribed for patients with androgenic alopecia, while 5 mg/d finasteride is prescribed for benign prostatic hyperplasia (BPH) given a patient with approximately 70 kg body weight. The amounts of finasteride for the injection were adjusted based on the weight of mice (20-25 g) [10]. Since mouse spermatogenic cycle usually takes 35 days, treatment course was set to last 35 days accordingly [11]. After the treatment period, mice were anesthetized with chloroform, and their testes and epididymis were removed. Isolated samples were fixed in formaldehyde for histological examinations. In addition, blood was taken from their hepatic vein [12].

Tissue samples were paraffin-embedded, sectioned by a microtome and placed on the slides. Finally, the samples were stained with hematoxylin-eosin and imaged under an optical microscope. The percentage of motile spermatozoa, sperm count in the epididymis, and the number of spermatogonial cells, primary spermatocytes, spermatocytes, and spermatozoids were determined in the histological evaluations [13].

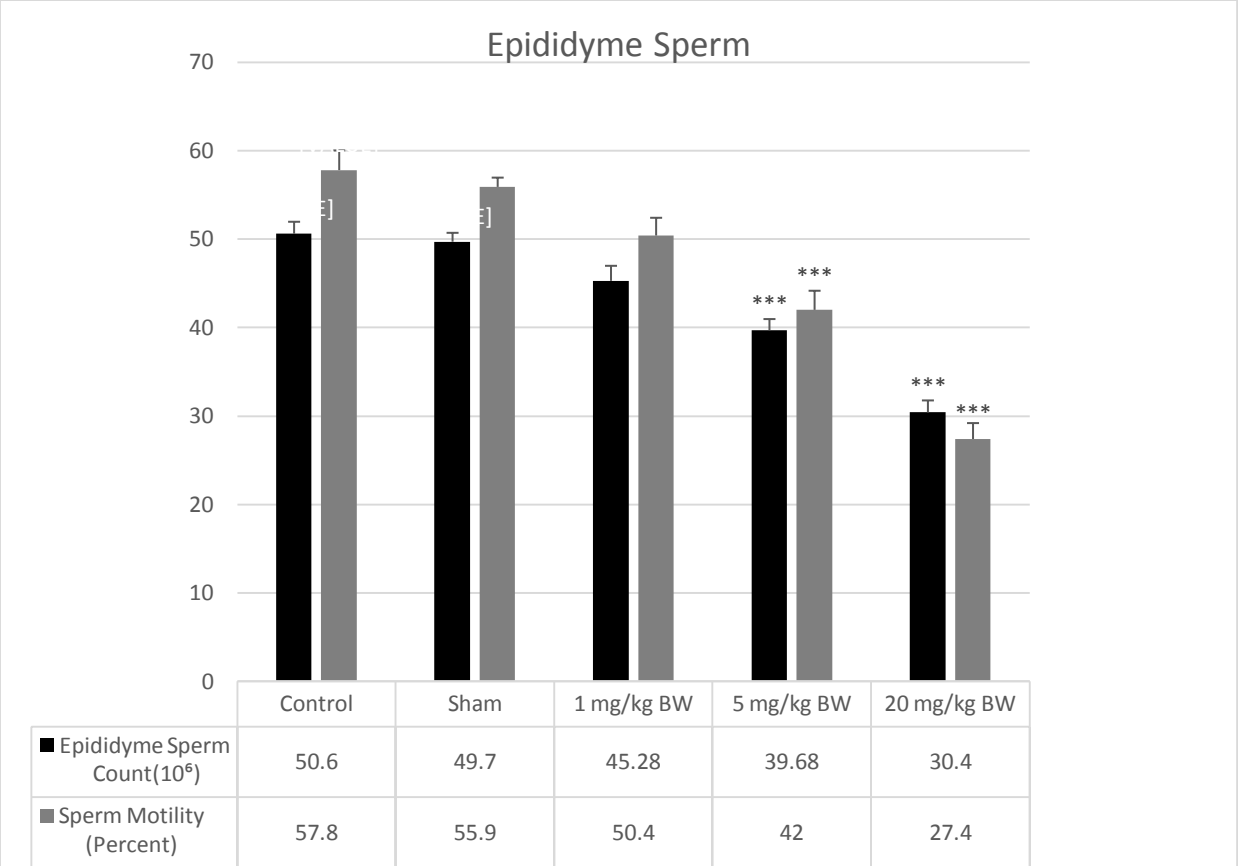
Moreover, the blood samples were centrifuged at 3000 rpm for twenty minutes. By the sampler, the blood serum was isolated. The isolated serum was transferred to a -20oc freezer for hormonal studies. The technique used for hormonal testing was the ELISA. This technique is based on the reaction of an antibody with an antigen [12].

Statistical calculations were performed using SPSS software at a significant level of P <.05 and one-way analysis of variance. Tukey test was performed and the relevant graphs were drawn by Excel software [9].

3. RESULTS

The number of normal sperm decreased in all experimental groups, but in the two groups of finasteride with doses of 20 mg/kg BW and 5 mg/kg BW, this decrease was significant (p <.001) (5 mg/kg BW: p=.00091, 20 mg/kg BW: p=.00066) (Chart 1).

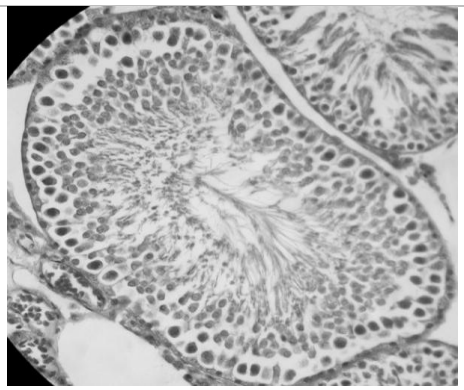
The sperm cell motility decreased in the epididymis. In the group of finasteride with a dose of 1 mg/kg BW, this decrease was not significant, but in the other two doses, this decrease was significant. There was a significant difference between the two groups of finasteride with doses of 5 and 20 mg/kg BW at the level of p <.001 (5 mg/kg BW: p=.00079, 20 mg/kg BW: p=.00046) (Chart 1).



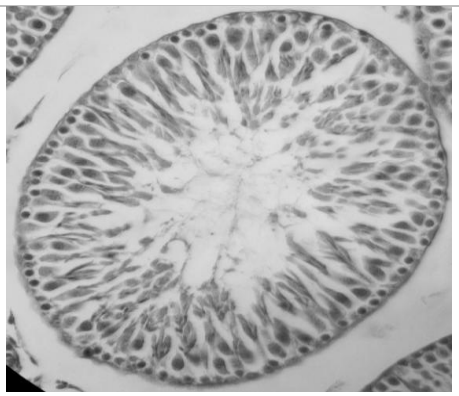
	Control	Sham	1 mg/kg BW	5 mg/kg BW	20 mg/kg BW
Epididyme Sperm Count(10^6)	50.6	49.7	45.28	39.68	30.4
Sperm Motility (Percent)	57.8	55.9	50.4	42	27.4

Chart 1: counts and motility of epididymal sperm in experimental and control groups. (*: Significant Difference P<.05, **: Significant Difference P<.01, ***: Significant Difference P<.001)

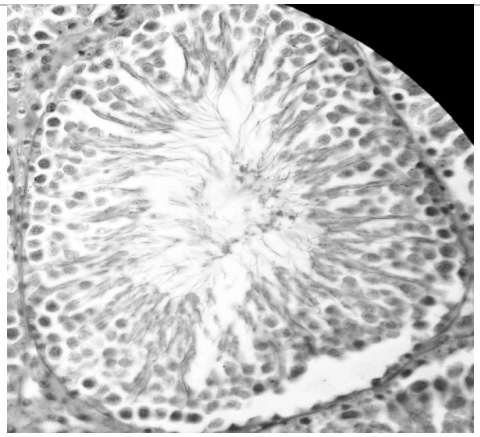
As figure 1 and chart 2 show, finasteride had a negative effect on the number of spermatogonia in testicular tissue. The rate of this decrease at two doses of 1 and 5 mg/kg BW was not statistically significant, but at the dose of 20 mg/kg BW, this decrease was significant (p <.001) (p=.00073).



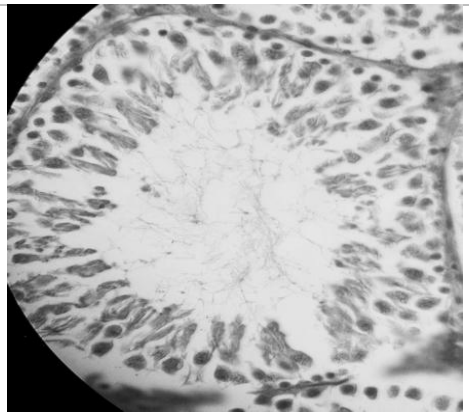
Control



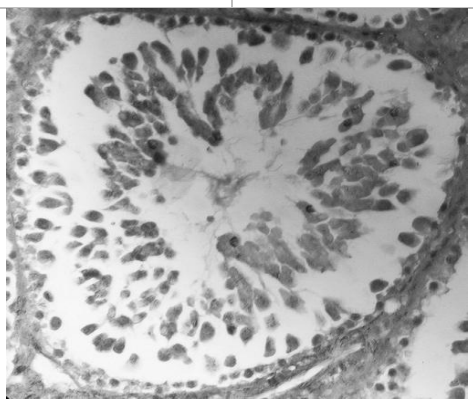
Sham



Finasteride 1 mg/kg BW

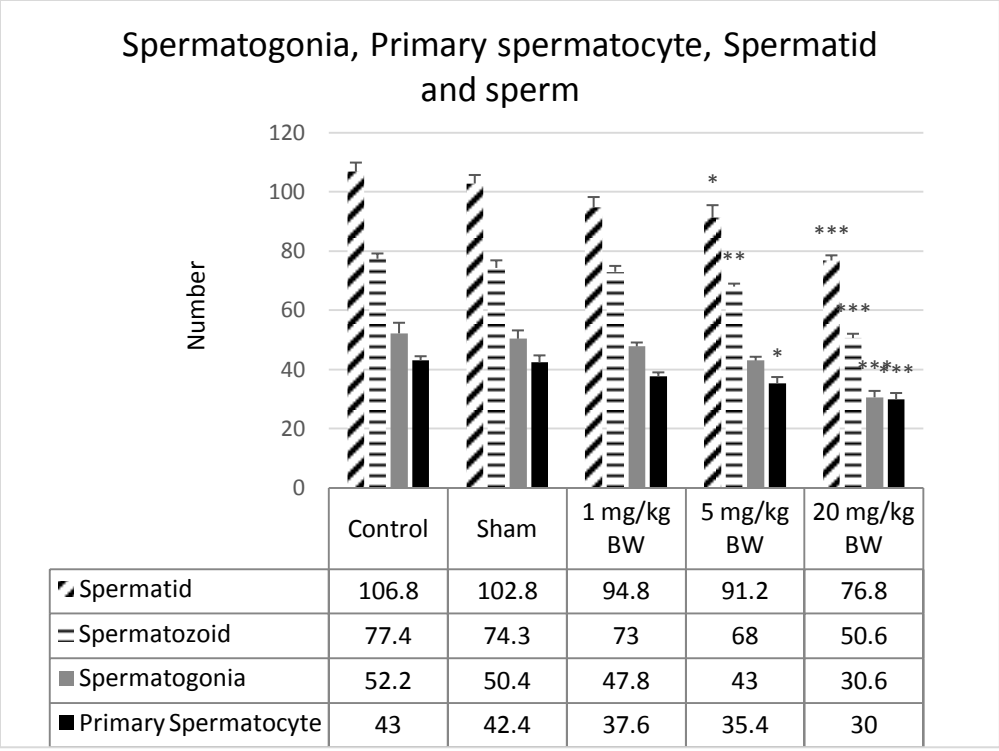


Finasteride 5 mg/kg BW



Finasteride 20 mg/kg BW

Figure 1: Micrograph of changes induced by the effect of finasteride on testicular tissue(400X).



	Control	Sham	1 mg/kg BW	5 mg/kg BW	20 mg/kg BW
Spermatid	106.8	102.8	94.8	91.2	76.8
Spermatozoid	77.4	74.3	73	68	50.6
Spermatogonia	52.2	50.4	47.8	43	30.6
Primary Spermatocyte	43	42.4	37.6	35.4	30

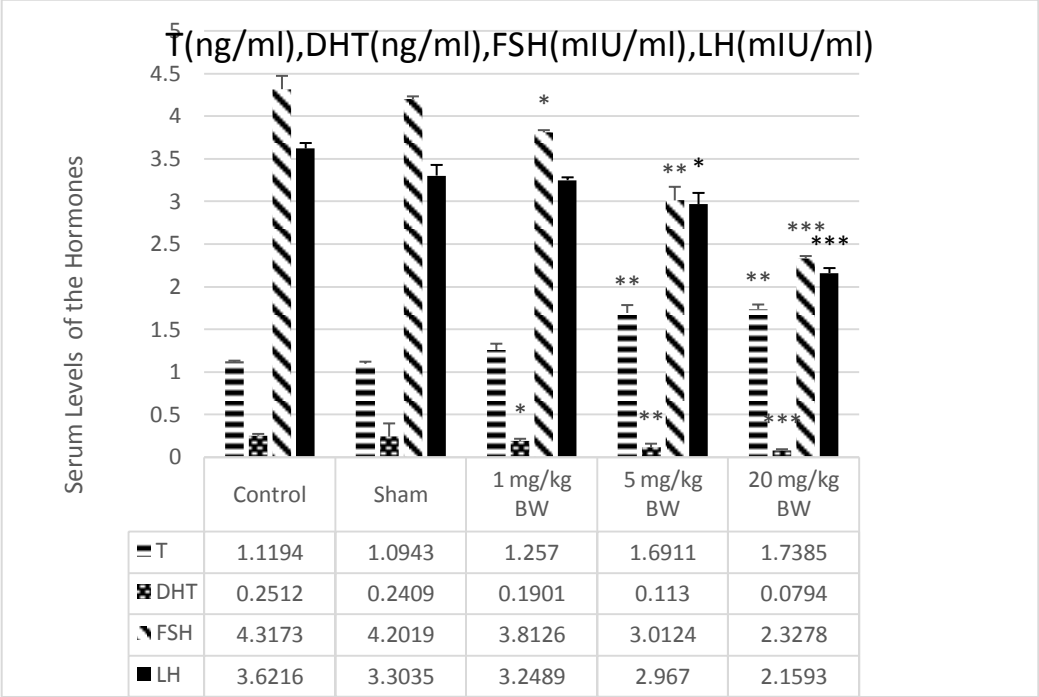
Chart 2: Counts of spermatogonia, primary spermatocyte, spermatid, testicular sperm in experimental and control groups. (*: Significant Difference P<.05, **: Significant Difference P<.01, ***: Significant Difference P<.001)

Finasteride lowered the number of primary spermatocytes in two experimental groups with higher injection dose. At a dose of 5 mg/kg BW, the level of this decrease was p <.05 (p=.014), but at a dose of 20 mg/kg BW, its level was p <.001 (p=.00089) (figure 1 and chart 2).

Based on figure 1 and chart 2, finasteride reduced spermatid cells in testicular tissue. At the dose of 1 mg/kg BW, its reduction was not statistically significant, but at a dose of 5 mg/kg BW was statistically significant p <.05 (p=.018) and at the dose of 20 mg/kg BW was p <.001(p=.00074).

Finally, sperm cells were counted in testicular tissue and analyzed. Two experimental groups receiving finasteride at doses 5 and 20 mg/kg BW were statistically significant. There was a significant difference at the level of p <.01 (p=.004) for the dose of 5 mg/kg BW and p <.001for the dose of 20 mg/kg BW (p=.00074) (figure1 and chart 2).

The results of ELISA test revealed that the level of testosterone increased in all three experimental groups and that in the two groups of 5 and 20 mg/kg BW these increases were statistically significant (5 mg/kg BW: p=.0081, 20 mg/kg BW: p=.0083). Interestingly, in the two groups, the increase rates were almost the equal and no significant increase was observed in T hormone in the 20 mg/kg BW group compared to the 5 mg/kg BW group (chart 3).



	Control	Sham	1 mg/kg BW	5 mg/kg BW	20 mg/kg BW
T	1.1194	1.0943	1.257	1.6911	1.7385
DHT	0.2512	0.2409	0.1901	0.113	0.0794
FSH	4.3173	4.2019	3.8126	3.0124	2.3278
LH	3.6216	3.3035	3.2489	2.967	2.1593

Chart 3: Levels of Hormones T (ng/ml), DHT (ng/ml), FSH (mIU/ml), LH (mIU/ml) in the blood serum of mice in the control group and different doses of finasteride

*: Significant difference with control group (p <.05), **: Significant difference with control group (p <.01) ***: Significant difference with control group (p <.001)

In addition, the amount of DHT in all experimental groups decreased significantly. This decrease was statistically significant even in the 1 mg/kg BW (P<.05) (p=.047). With increase in the amount of finasteride injection in the three experimental groups, the level of DHT in the blood serum of the samples decreased. However, the findings showed that the level of FSH in the experimental groups also underwent significant changes. The level of this hormone decreased significantly in all three groups. In the study of LH levels in the blood serum of mice, a decreasing trend was observed, but this decrease was statistically significant in the two groups of 5 and 20 mg/kg BW only (5 mg/kg BW: p=.032, 20 mg/kg BW: p=.00093) (chart 3).

4. Discussion

Tissue Studies

According to the histological results obtained in this study, the number and motility of epididymal sperm in experimental groups with doses of 5 and 20 mg/kg BW were significantly reduced. Also, a significant negative effect on the number of spermatogonia was observed in the group with a dose of 20 mg/kg BW. The results indicated that finasteride had a decreasing effect on the number of primary spermatocytes, spermatid, and sperm cells in testicular tissue. These decreases were significant in two groups with doses of 5 and 20 mg/kg BW.

In the 1990s, Steiner et al. studied the effect of different doses of finasteride on the number of sex cells in the testes of men, which demonstrated a significant decrease in the number of sex cells [14]. A 2012 study found that claudin-11 expression depends on DHT levels, which play an important role in the formation of calcium bonds between Sertoli cells and the formation of a testicular-blood barrier. Decreased DHT hormone negatively affects the quality of this structure and can cause an immune system attack on haploid cells in the testis. This study was conducted on male rats [15]. According to the results of the present study in which sperm lesions and their reduction were observed, the reason can be the possible side effects of DHT reduction and its adverse effects on Sertoli cells and the testicular-blood barrier.

Garcia also reported in 2012 that 30 days of taking the drug could cause many negative morphological outcomes in sperm, highlighting epididymal damage and sperm quality and function. The results of this study are consistent with the findings of the present study, especially considering epidemic sperm [16]. Research on the effect of reducing the enzyme 5α - Reductase on spermatogenesis indicates that reduction of this enzyme has negative effects on the process. These negative effects are especially greater in the repair and the progression of the middle stages of meiosis. The reduction of this enzyme and DHT hormone reduces the adhesion of round spermatozoa to Sertoli cells and reduces the final product of spermatogenesis by twenty to forty percent. Based on this study, a hypothesis has been proposed: development of spermatogenesis in stages seven and eight of meiosis, in which secondary spermatocytes become spermatids, is largely dependent on the hormone DHT [17].

A 2002 study carried out in Brazil revealed that the use of finasteride was ineffective in the process of spermatogenesis. This study was performed on Wistar rats [18]. In 2001, researchers in Canada reported that finasteride had no significant effect on spermatogenesis or pregnancy. This study was experimentally conducted on humans [19]. A 2001 study found that low-dose finasteride had no effect on semen or spermatogenesis. The study was done on young men [20].

A 2004 study about the effects of 5α-reductase on various tissues in the body reported that this enzyme plays an important role in repairing and improving the function of fibroblast cells. The important role of these cells in the health of sperm cells and spermatozoa and various parts of the testicular structure such as the testicular blood barrier can indicate the important role of this enzyme in the optimal function of spermatogenesis [21]. In a study, it was found that the DHT hormone has a great role in sperm-producing and efferent tubules, especially the epididymis, and leads to the final development and optimal maintenance of sperm cells. Reducing it to finasteride can definitely cause movement disorders and sperm cell viability [22]. Another study on the side effects of an androgen inhibitor found that a decrease in DHT in the testicles of adult men reduced cell transplants occurred in the tubes and ducts but had a greater effect on the epididymis [23].

According to the results of the above-mentioned studies, it can be summarized that the decrease of DHT hormone causes damage to the epididymis, seminiferous ducts, cell connections between Sertoli cells and damage to the blood testicular barrier. Inhibition of the 5α-reductase enzyme also has a negative effect on meiotic division, causing damage to fibroblast cells in the testis. A combination of these factors and

possible mechanisms can cause tissue damage to sex cells in the testis, which is consistent with the results of our research.

Hormonal Studies

According to the Hormonal results obtained in this study, the level of testosterone increased numerically in all three experimental groups, but only in the two groups of 5 and 20 mg/kg BW was statistically significant. The levels of DHT decreased significantly in all three experimental groups. The level of FSH went down in all three experimental groups and was statistically significant. The level of LH went down in all three experimental groups, but was statistically significant in only two groups with doses 5 and 20 mg/kg BW.

In a 1998 clinical study on middle-aged men, Uygur examined the effect of this drug at a dose of 5 mg/kg BW on the secretion of gonadotropins, testosterone and dihydrotestosterone. His research showed a sharp decrease in hormones such as LH and FSH but an increase in serum testosterone levels. The findings of this research are in line with those of our study[24]. Also, in a study conducted on a population of men taking this drug at a dose of 5 mg/kg BW, the negative effect of this drug on fertility was reported. In this study, the effect of this drug on semen factors and the amount of sex hormones in blood serum was investigated, but gonadotropin hormones were not studied [25]. In 2015, an interesting study in a population of men reported that smoking marijuana, despite increasing testosterone levels, reduced spermatogenesis and related parameters. This report showed that elevated serum testosterone levels do not necessarily lead to spermatogenesis [26].

In a 1996 study of the effects of finasteride on humans, it was argued that although DHT levels decreased and T levels increased, there was no change in the levels of other sex hormones [27]. In 2001, Amory et al. stated in a study that taking finasteride, 5α-reductase inhibitors had no effect on sex hormone levels or semen parameters [28]. A 2005 study on rats in South Korea found that low-dose finasteride had no significant effect on spermatogenesis or Pituitary-Testicular Hormone Axis [29].

A report in the 1990s indicated that enzyme 5α-reductase is highly active in the testes of male rats and that the regulation of the production of this enzyme is related to the interaction of gonadotropins [30]. Another study emphasizes the direct and indirect effects of the enzyme feedback on the hormonal secretions of the pituitary gland, especially gonadotropins [2531]. Another study has revealed the regulatory effects of this enzyme on LH secretion, hypothesizing that this enzyme has an effect on Leydig cells and the pituitary gland [2632]. In 2013, a study found that in mice the enzyme type 5α-reductase type 2, as a neurosteroid, performs important activities in neurological, behavioral, and hormonal secretion. finasteride can also lead to complex neurohormonal disorders by inhibiting this enzyme by crossing the blood-brain barrier [33]. Another 2008 study in Japan came to the conclusion that the drug inhibited the 5α-reductase enzyme in the brain, causing complex hormonal disorders in a group of hormones, especially steroid hormone [34]. Recent research has underscored the important effects of this enzyme on hypothalamic activity in the brain, metabolism of sex hormones, regulation of sexual behaviors and affecting sex hormone receptors, and effects on organs such as the liver and thyroid gland [35. 36].

Given these findings, it seems that decrease in DHT is due to inhibition of the enzyme 5α-reductase, thus increasing the hormone T in the blood serum. finasteride also inhibits the enzyme 5α-reductase type 2 by crossing

the blood-brain barrier, which has many effects on the hypothalamus, pituitary gland and secretion of LH and FSH gonadotropins. The combination of these factors and possible mechanisms can disrupt the secretion and amount of the four desired hormones in the blood serum, consistent with the results of our test.

5. Conclusion

Overall, it is speculated that finasteride at a dose of 5 mg/kg BW and more might have side effects on the male reproductive ability and spermatogenesis.

Although based on the evidence, low- or short-term use of this drug has not had a negative effect, it can have significant side effects on people who suffer from fertility problems. Due to the effects of this drug on testicular tissue and secretion of hormones involved in the reproductive system especially in different stages of spermatogenesis, the possibility of adverse effects is expected more and this should be considered in long-term use of finasteride. However, further research is needed as for the effects of finasteride as well as the long-term effects of taking its low-dose. In addition to the above, it is necessary to delve into the long-term effects of this drug after stopping its use.

Statement of Ethics

The present study was approved by the ethics committee with the ethical code of IR.IAU.SRB.REC.1398.195. All the experimental steps followed the ethical guidelines of the local committee.

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Conflict of interest

The authors reported no conflict of interest.

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