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The role of SRD5A2 enzyme levels and activity in infertile men in Tikrit, Iraq

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ABSTRACT

Male infertility, impacting 40-50% of couples globally, encompasses various classifications such as azoospermia, oligozoospermia, asthenozoospermia, and azoospermia. The 5α-reductase Type 2 (SRD5A2) enzyme has been implicated in regulating spermatogenesis and androgen metabolism, but its role in male infertility remains unclear. This study aimed to clarify the potential role of SRD5A2 as a biomarker for male infertility and to explore the correlation between the SRD5A2 enzyme and other hormones in the seminal fluid of Iraqi men with various infertility conditions (asthenozoospermia, oligozoospermia, and azoospermia). A total of 90 male participants aged 20-40 were categorized into four groups: asthenozoospermia (24), oligozoospermia (24), azoospermia (18), and normozoospermia (24). Serum and seminal plasma samples were collected for evaluation of SRD5A2 activity, SRD5A2 levels and some hormonal levels using ELISA. Significantly lower SRD5A2 activity and levels were observed in infertile groups compared to normozoospermic men. A significant negative correlation was observed between SRD5A2 activity and DHT in the asthenozoospermia and azoospermia groups. In the asthenozoospermia group, a significant positive correlation was observed between DHT and SRD5A2 levels. This study showed that changes in SRD5A2 activity and levels were associated with male infertility subtypes. The SRD5A2 enzyme plays a crucial role in spermatogenesis and in male infertility.

Keywords: SRD5A2 enzyme, Male infertility and Spermatogenesis

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دور مستوى ونشاط أنزيم SRD5A2 في الرجال المصابين بالعقم في مدينة تكريت، العراق

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الملخص

يشمل العقم عند الذكور، الذي يؤثر على 40–50٪ من الأزواج على مستوى العالم، تصنيفات مختلفة مثل فقد النطاف، وقلة النطاف، ووهن النطافية، وفقد النطاف. يشترك إنزيم 5α-Reductase Type 2 (SRD5A2) في تنظيم تكوين السائل المنوية واستقلاب الأندروجين، لكن تفاعلها في العقم عند الذكور لا يزال غير واضح. لذلك، تهدف هذه الدراسة إلى توضيح الدور المحتمل ل SRD5A2 كمؤشر حيوي للعقم عند الذكور واستكشاف العلاقة بين إنزيم SRD5A2 مع الهرمونات الأخرى في السائل المنوي للرجال العراقيين الذين يعانون من حالات العقم المختلفة (وهن المنوية، قلة النطاف، وفقد النطاف). تم تصنيف ما مجموعه 90 مشاركا من الذكور الذين تتراوح أعمارهم بين 20 و40 عاما إلى أربع مجموعات: وهن النطاف (24)، وقليل النطاف (24)، وفقد النطاف (18)، طبيعي النطف (24). تم جمع عينات المصل والبلازما المنوية لتقييم نشاط SRD5A2، ومستويات SRD5A2، ومستويات بعض الهرمونات باستخدام تقنية ELISA. لوحظ انخفاض ملحوظ في نشاط SRD5A2 ومستوياته في مجموعات العقم مقارنة بمجموعة الرجال طبيعي النطف. لوحظ وجود علاقة سلبية ذات دلالة إحصائية بين نشاط SRD5A2 و DHT في مجموعة وهن النطف وفقد النطاف. بينما، في مجموعة وهن النطف، لوحظ ارتباط إيجابي كبير بين مستويات DHT ومستويات SRD5A2. أوضحت هذه الدراسة أن التغيير في نشاط SRD5A2 ومستوياته كان مرتبطا بأنواع فرعية من العقم عند الذكور. لذلك، يلعب إنزيم SRD5A2 دورا مهما في تكوين المنوية والعقم عند الذكور

INTRODUCTION

Male infertility is recognized as a significant public health concern; it results in the inability of couples to conceive following unprotected sexual intercourse for a minimum duration of 12 months after marriage. [(1)]. It represents roughly 40-50% of global infertility instances. [(2)]. Cases of male infertility can be categorized into four principal classifications: male-related factors, female-related factors, combined factors, and instances of unexplained infertility. [(3, 4)]. Depending on the analysis of semen, male infertility is divided into several types, such as oligozoospermia (low sperm count), azoospermia (sperm absence), asthenozoospermia (impaired sperm motility), and teratozoospermia (abnormal semen morphology) [(5)]. Enzymes perform important and complex functions in male infertility, including modifying hormonal pathways, lipid peroxidation, and oxidative stress. [(6)].

The steroid SRD5A plays a central role in external genitalia development, male prostate and is vital for sperm maturation predominantly in the epididymis post-puberty by converting testosterone to dihydrotestosterone (DHT) [(7, 8)]. SRD5A includes two isoenzymes: SRD5A1 type 1, which is found in the skin, ovary, and brain, and SRD5A2 type 2, which is restricted to the epididymis, seminal vesicles, genital skin, uterus, breast, hair follicle, and placenta [(9)]. The SRD5A2 enzyme is produced by the SRD5A2 gene, located on chromosome 2 (2p23). This gene comprises five exons and four introns and encodes a 254-amino-acid protein. Alterations in this gene underlie a specific subset of differences in sex development (DSD) observed in individuals with a 46, XY karyotype [(10)]. The genetic difference observed within the SRD5A2 gene can modify either the expression levels or the functional activity of the 5α-reductase enzyme it

encodes [11]. The entirety of the genetic disparities indicates that variations in SRD5A2 are associated with an elevated likelihood of developing pathologies of the male reproductive organs and their functions [12]. The diminished functionality of the SRD5A2 enzyme leads to inconsistent deficits in DHT production, contingent on its remaining activity, a condition known as 5α-Reductase type 2 deficiency, an autosomal recessive disorder resulting from mutations or polymorphisms in the SRD5A2 gene [13].

So, this study aims to explore the potential role of the SRD5A2 enzyme in three types of male infertility, as asthenozoospermia, oligozoospermia and azoospermia in men in the Tikrit population, Iraq.

MATERIALS AND METHODS

Study Population

This study involved 90 male participants aged 20 to 40, including 24 with asthenozoospermia, 18 with oligozoospermia, 24 with azoospermia, and 24 with normozoospermia, all of whom had demonstrated fertility by fathering children. Each participant underwent an extensive evaluation of semen parameters. The exclusion criteria encompassed tobacco consumption, exposure to environmental or occupational toxins, sexually transmitted infections, cryptorchidism, genitourinary anomalies, and surgical procedures for infertility treatment.

Sample Collection

Two distinct sample types were obtained from each participant following three days of sexual abstinence, involving five mL of venous blood collected in a gel tube for serum separation to assess enzyme and hormone profiles. And seminal specimens were allowed to liquefy for 30 minutes at 37 °C, and subsequently processed in accordance with the World Health Organization's 2010 protocols.[14]. Centrifugation of seminal samples was performed for 10 minutes at 500 rpm, after which the supernatant (seminal plasma) was transferred to an Eppendorf tube.

ELISA assay

Serum and seminal samples were used to assess enzyme and hormonal levels using ELISA kits from Sunlong, China, according to the provided instructions.

Statistics Analysis

GraphPad Prism version 10. served as a tool for conducting a thorough statistical analysis. The results are expressed as mean ± standard deviation. To compare statistical variations across multiple groups, we utilized a one-way analysis of variance (ANOVA), ensuring reliable comparisons. Additionally, we employed Pearson's correlation analysis to calculate the correlation coefficient, which indicates the strength and direction of the linear relationship between two variables. A p-value of less than 0.05 reveals statistically significant findings.

RESULTS AND DISCUSSION

Serum levels of SRD5A2, FSH, and LH.

The data presented in Figure 1 provide a comprehensive overview of the average levels of serum indicators, including SRD5A2 enzymatic activity, FSH, and LH, across four distinct categories of male subjects: asthenozoospermia, oligozoospermia, azoospermia, and normozoospermia.

The examination of serum SRD5A2 enzymatic activity across various classifications of male fertility disclosed noteworthy disparities. The average SRD5A2 activity in men with asthenozoospermia was 55.653 ± 4.338, whereas in those with oligozoospermia, it was 54.178 ± 4.680. Men presenting with azoospermia exhibited a mean activity of 54.581 ± 3.414, in stark contrast to normozoospermic men, who showed the highest mean value at 57.948 ± 4.967. Statistical analyses demonstrated a significant difference among the groups ($P \leq 0.05$), suggesting that SRD5A2 activity may influence male fertility status.

The hormonal profiles of the four male cohorts were examined, revealing notable discrepancies in FSH concentrations. The average FSH concentrations for asthenozoospermia, oligozoospermia, azoospermia, and normozoospermia were recorded at 4.588 ±

0.95, 4.649 ± 0.451, 4.871 ± 0.276, and 4.573 ± 0.354, respectively. Statistical evaluation demonstrated no significant differences among the cohorts (p = 0.363). These results imply that FSH concentrations may not serve as a definitive distinguishing factor among the various types of male infertility investigated in this research.

The average levels of LH were markedly reduced in the asthenozoospermia cohort (45.926 ± 9.08 ng/L) when juxtaposed with the oligozoospermia 49.159 ± 2.842 and azoospermia cohorts 50.343 ± 3.116, as well as the normozoospermia cohort 50.376 ± 4.662, yielding a p-value of ≤ 0.05. Such results suggest that LH concentrations may be implicated in the pathophysiology of male infertility, especially in the context of asthenozoospermia. Additional investigations are necessary to elucidate the fundamental mechanisms involved.

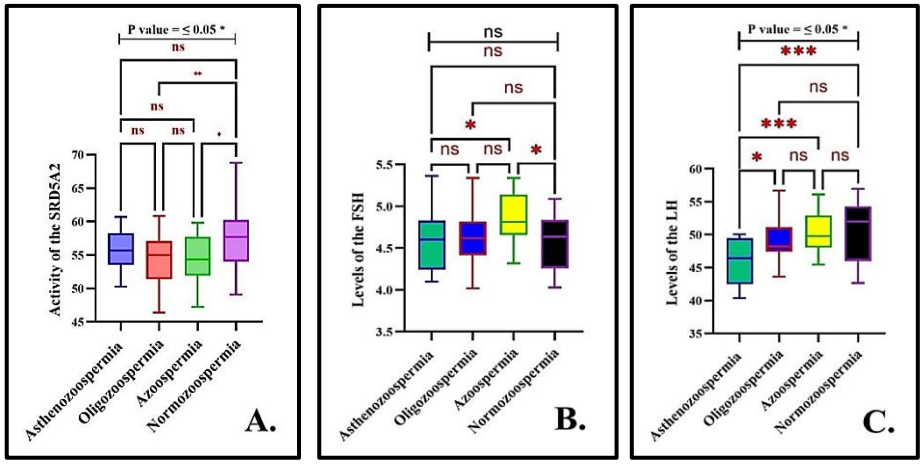

Fig. 1: Levels of serum biochemical parameters within the study cohort, (A) SRD5A2, (B) FSH and (C) LH comprising asthenozoospermia (n= 24), oligozoospermia (n= 24), azoospermia (n= 18), and normozoospermia (n= 24). The ANOVA test indicated significance at *: p ≤ 0.05, **: p ≤ 0.01, ***: p ≤ 0.001.

The absence of variation in follicle-stimulating hormone (FSH) concentrations in men with infertility can be attributed to several fundamental physiological mechanisms. Functional hypogonadotropic hypogonadism (FHH), a medical condition marked by compromised functioning of the hypothalamic-pituitary-gonadal axis, leads to diminished testosterone levels and infertility, frequently occurring without significant changes in gonadotropin levels, including FSH. [15]. Excessive adiposity and metabolic syndrome, commonly observed in males with infertility, may result in hormonal dysregulation characterized by elevated estrogen levels alongside diminished testosterone, LH, and FSH concentrations, thereby exacerbating the hormonal milieu without necessarily producing significant changes in FSH levels. [16]. Furthermore, the involvement of aquaporins in testicular cell metabolism and their relationship with sex hormones suggest that metabolic anomalies may influence testicular function and infertility independent of direct effects on FSH concentrations. [17]. Genetic determinants are also of paramount importance, with a considerable percentage of male infertility instances attributed to genetic causes; however, numerous cases remain enigmatic owing to the intricate nature of gene-disease interactions and the lag in the implementation of next-generation sequencing methodologies. [18].

Reduced LH concentrations in men with infertility can be ascribed to a multitude of factors, chiefly perturbations in the hypothalamic-pituitary-gonadal (HPG) axis. Functional hypogonadotropic hypogonadism (FHH) represents a clinical syndrome marked by dysfunction of the HPG axis, resulting in diminished levels of testosterone and gonadotropins, including LH, frequently linked

with conditions such as obesity, diabetes, and the administration of specific pharmacological agents like opioids and glucocorticoids[19]. Similarly, congenital hypogonadotropic hypogonadism (CHH), an uncommon condition attributed to a deficiency in gonadotropin-releasing hormone (GnRH), leads to diminished LH levels because GnRH is essential for LH synthesis [19, 20]. Environmental determinants, including prolonged exposure to polystyrene microplastics, have been shown to reduce LH concentrations by disrupting the LH-mediated LHR/cAMP/PKA/StAR signaling cascade, which is essential for testosterone biosynthesis and spermatogenesis [21]. Moreover, lifestyle determinants such as obesity and inadequate dietary practices may contribute to hormonal dysregulation, including diminished LH levels stemming from perturbations in the hypothalamic-pituitary-gonadal (HPG) axis and elevated estrogen concentrations, which exert negative feedback on LH synthesis [16].

Seminal plasma parameters levels of the study group

The data presented in Figure 2 delineate the mean concentrations of seminal plasma variables, including exosomes, DHT, protein carbonyls, Total antioxidant capacity, and malondialdehyde, across four distinct cohorts of male subjects: those diagnosed with asthenozoospermia, oligozoospermia, azoospermia, and normozoospermia.

The average levels of SRD5A2 exhibited statistically significant variations among the four studied groups. Males diagnosed with asthenozoospermia displayed an average SRD5A2 concentration of 735.569 ± 45.287. Conversely, males with oligozoospermia had a higher average concentration of 946.026 ± 129.024, whereas those with azoospermia had even higher levels at 1244.234 ± 131.381. The normozoospermia cohort had the highest mean SRD5A2 concentration at 1466.501 ± 165.255 pg/ml. A comparative analysis of these concentrations revealed a statistically significant difference ($p \leq 0.05$), suggesting that SRD5A2 levels increase as sperm quality declines, with individuals classified as normozoospermic demonstrating the highest levels.

The hormonal assessment revealed significant differences in dihydrotestosterone (DHT) concentrations across distinct cohorts of men with diverse sperm characteristics. The average DHT levels in men with asthenozoospermia were 1.636 ± 0.12, whereas those with oligozoospermia were 1.735 ± 0.100. Males diagnosed with azoospermia exhibited a marginally lower average DHT concentration of 1.701 ± 0.125, while normozoospermic males had the lowest average at 1.595 ± 0.150. Statistical analyses revealed a significant difference among the groups ($P \leq 0.05$), suggesting a possible association between DHT concentrations and sperm quality parameters.

In contrast to SRD5A2 and DHT, there were no statistically significant differences in free testosterone concentrations across the studied cohorts. The average free testosterone concentrations were 45.571 ± 1.689 pmol/L in males with asthenospermia, 46.853 ± 2.768 pmol/L in individuals with oligospermia, 47.149 ± 3.282 pmol/L in azoospermic males, and 45.853 ± 3.119 pmol/L in the normospermic cohort. The statistical analysis yielded a p-value of 0.178, indicating no significant differences in free testosterone concentrations among the groups. This observation implies that although SRD5A2 and DHT levels correlate strongly with sperm quality, free testosterone levels may not be instrumental in distinguishing these conditions.

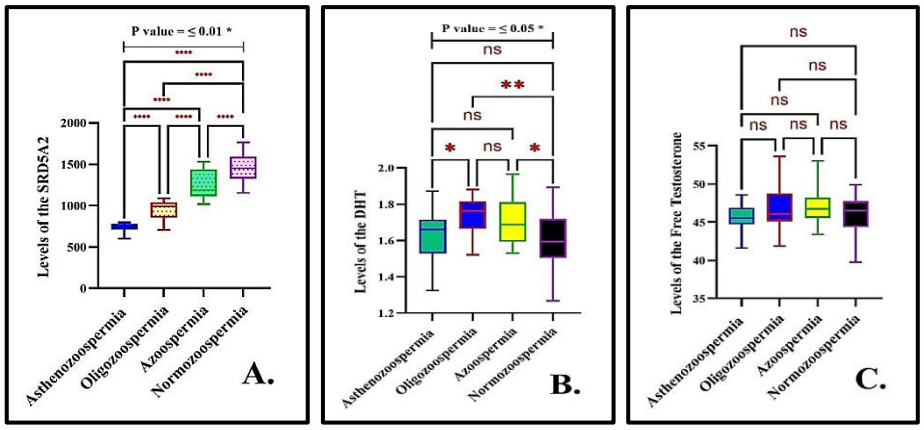

Fig. 2: Levels of seminal plasma parameters in the study cohort, (A) SRD5A2, (B) DHT, (C) free testosterone, which includes asthenozoospermia (n= 24), oligozoospermia (n= 24), azoospermia (n= 18), and normozoospermia (n= 24). The results were analyzed using ANOVA, with significance denoted as *: p ≤ 0.05, **: p ≤ 0.01, ***: p ≤ 0.001.

SRD5A2 levels gradually increase from asthenozoospermia to azoospermia, with normal sperm samples showing the highest levels, suggesting a role in male infertility. Variations in SRD5A2, which converts testosterone to DHT, may impact sperm quality and quantity, and the significant differences across groups highlight its link to sperm motility and count. [8].

Infertile men often have reduced SRD5A2 enzyme levels mainly due to mutations in the SRD5A2 gene, which can cause sexual development disorders in individuals with 46, XY. Conversely, higher SRD5A2 levels in azoospermia are usually affected by genetic and environmental factors.[22]. Environmental influences, especially chemicals that disrupt endocrine function, are believed to affect how 5α-reductase type 2 deficiency presents clinically by altering hormonal signaling, potentially leading to greater differences in physical traits. For instance, exposure to these chemicals before birth has been linked to heightened estrogen activity, potentially impacting genital development and overall developmental results.[23]. Additionally, external stressors such as oxidative harm caused by pollutants and chemicals can disrupt hormonal balance, potentially affecting the presentation and severity of hypogonadism and related disorders. [24]. The consistent testosterone levels observed in infertile men can be attributed to several physiological processes, notably disruptions in the hypothalamic-pituitary-gonadal axis. An example of this is the "Exercise-Hypogonadal Male Condition" (EHMC), in which prolonged endurance exercise results in reduced testosterone without affecting LH levels. This pattern suggests a regulatory imbalance rather than a direct defect in testosterone production. [25]. Leydig cell dysfunction, frequently associated with seminiferous tubule impairment, exacerbates testosterone synthesis, likely attributable to disrupted intratesticular signaling mediated by activin and inhibin. [26]. Additionally, metabolic syndrome, common in infertile males, exacerbates oxidative stress and endothelial dysfunction, adversely affecting testosterone synthesis and semen quality. [27]. Moreover, pathological conditions like varicocele may adversely affect Leydig cell functionality; however, surgical procedures such as varicocelectomy have demonstrated efficacy in enhancing testosterone concentrations, especially in individuals with hypogonadism, indicating that anatomical abnormalities can also influence testosterone homeostasis. [28].

Correlation coefficient analysis between SRD5A2 activity and levels with other parameters:

The heat map in Figure 3 illustrates the relationship between SRD5A2 enzymatic activity and four hormonal levels (DHT, Testosterone, FSH, and LH)

across four categories of semen analysis (Asthenozoospermia, Oligozoospermia, Azoospermia, and Normozoospermia). A notable inverse relationship was found between SRD5A2 activity and DHT in both the asthenozoospermia group (r = -0.4749, p = 0.0190) and the azoospermia group (r = -0.6158, p = 0.0065), while no significant associations existed for testosterone, FSH, or LH, suggesting that SRD5A2 activity is predominantly linked to DHT levels in asthenozoospermia and azoospermia; additionally, a significant positive correlation between DHT and SRD5A2 was noted in the asthenozoospermia group (Pearson r = 0.5255, P = 0.0084).

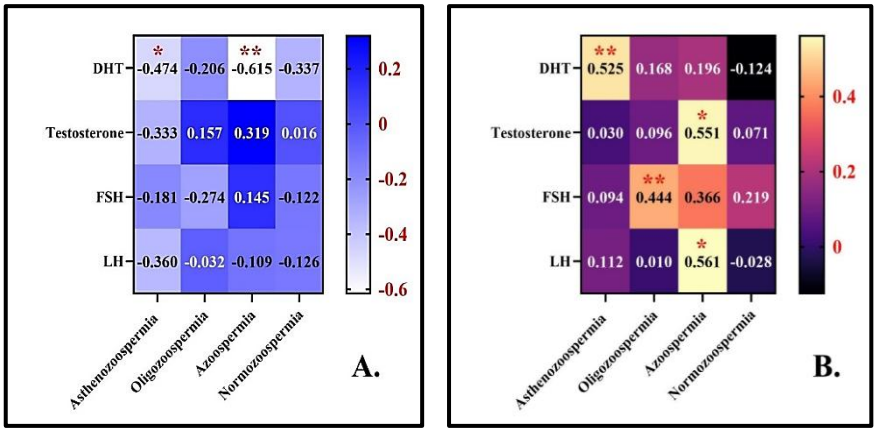

Fig. 3. Heat maps illustrating the correlation coefficients are presented. A. The correlation coefficient between the average SRD5A2 activity and various parameters of the study cohorts. B. The correlation coefficient for mean SRD5A2 levels with other parameters within the study groups.

In the oligospermia cohort, a significant positive correlation was observed between FSH and SRD5A2 levels (Pearson r = 0.4449, P = 0.0294), while other hormones showed no notable associations. Conversely, in the azoospermia group, significant correlations with testosterone (Pearson r = 0.5513, P = 0.0177) and LH (Pearson r = 0.5613, P = 0.0154) levels were identified, indicating that SRD5A2 may be particularly pertinent to asthenozoospermia and azoospermia, thus necessitating further research on its implications for male fertility.

The inverse relationship between SRD5A2 enzymatic activity and dihydrotestosterone (DHT) levels in male infertility is fundamentally linked to SRD5A2's role in testosterone conversion to DHT, an essential androgen for male sexual maturation and reproductive capability, with mutations in SRD5A2 potentially causing 5α-reductase type 2 deficiency and resulting in diminished DHT production, leading to male pseudohermaphroditism characterized by ambiguous genitalia alongside a standard male internal urogenital system.[22]. The catalytic efficiency of the enzyme depends on its structural integrity, as evidenced by the crystal structure of SRD5A2, which reveals a distinctive topology critical to its function; mutations in pivotal residues such as E57 and Y91 may diminish enzyme activity and, consequently, lower DHT synthesis. [29]. A deficit in DHT compromises the integrity of the seminiferous epithelium, leading to accelerated germ cell loss and diminished fertility, as evidenced by animal studies. [30]. The expression of SRD5A2 and the distribution of local DHT are essential for cell proliferation in the periurethral mesenchyme, with DHT acting as an inhibitory factor during urethral development. [31]. Genetic diversity in SRD5A2, characterized by multiple allelic forms, plays a significant role in phenotypic variation in individuals with 5α-reductase deficiency, influencing external genital virilization and shaping sex assignment and gender identity. [32].

CONCLUSION

In summary, this study demonstrated a notable reduction in both SRD5A2 levels and functionality

in infertile males, along with a significant inverse relationship between SRD5A2 and DHT. So, alterations in the activity and levels of SRD5A2 are correlated with various subtypes of male infertility. These results underscore the regulatory function of SRD5A2 in spermatogenesis and its potential utility as both biomarkers and therapeutic targets for male infertility.

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Author contributions: The authors contributed equally to the study.

REFERENCE

1. Mohammad FG, AL-Azzawie AF. Assessment of Inhibin-B hormone level and its relationship with some gonadal hormones in males having idiopathic infertility. Tikrit Journal of Pure Science. 2021;26(2):41-7. https://doi.org/10.25130/tjps.v26i2.117 .

2. Akilah Amira A, Kabel Ahmed M, Alharthi Huda A. New perspectives in male infertility. GSC Biological and Pharmaceutical Sciences. 2017;1(3):12-9. https://doi.org/10.30574/gscbps.2017.1.3.0027 .

3. Mahdi MA, Shwish DL, Almhmdi NA. Evaluation of the impact of the level of (Testosterone, Luteinizing Hormone, Follicle-Stimulating Hormone and Prolactin) on some semen parameters in infertile males. Tikrit Journal of Pure Science. 2018;23(7):27-31. https://doi.org/10.25130/tjps.v23i7.691 .

4. Manssor ARJ, Al–Mahdawi ZMM, Hadi AM. The effect of L-Arginine on the treatment of infertile men on semen parameters. Tikrit Journal of Pure Science. 2019;24(5):1-4. https://doi.org/10.25130/j.v24i5.858 .

5. He X, Yang S, Lv M. Genetic factors in male infertility. Frontiers Media SA; 2023. p. 1187445. https://doi.org/10.3389/fgene.2023.1187445 .

6. Alahmar AT, Calogero AE, Singh R, Cannarella R, Sengupta P, Dutta S. Coenzyme Q10, oxidative stress, and male infertility: A review. Clinical and experimental reproductive medicine. 2021;48(2):97. https://doi.org/10.5653/cerm.2020.04175 .

7. Elzanaty S, Giwercman Y, Giwercman A. Significant impact of 5α-reductase type 2 polymorphisms on sperm concentration and motility. International journal of andrology. 2006;29(3):414-20. https://doi.org/10.1111/j.1365-2605.2005.00625.x .

8. Mohammad FG, Al-Azzawie AF. Assessment of steroid 5 alpha reductase enzyme levels and their correlation with sex hormones in infertile Iraqi men. International Journal for Research in Applied Sciences and Biotechnology (IJRASB). 2020;7(6):227-33. https://doi.org/10.31033/ijrasb.7.6.32 .

9. Pekkolay Z, Kılıç F, Tuzcu ŞA, Soylu H, Tuzcu AK. 5-Alpha Reductase Deficiency: A Review of Five Cases Diagnosed with Ambiguous Genitalia. Turkish Journal of Endocrinology and Metabolism. 2017;21(2):60. https://doi.org/10.25179/tjem.2017-56481 .

10. Batista RL, Mendonca BB. The molecular basis of 5α-reductase type 2 deficiency. Sexual Development. 2022;16(2-3):171-83. https://doi.org/10.1159/000525119 .

11. Ellis JA, Panagiotopoulos S, Akdeniz A, Jerums G, Harrap SB. Androgenic correlates of genetic variation in the gene encoding 5α-reductase type 1. Journal of Human Genetics. 2005;50(10):534-7. https://doi.org/10.1007/s10038-005-0289-x .

12. Zhao D, Wu W, Xu B, Niu X, Cui H, Zhang Y, et al. Variants in the SRD5A2 gene are associated with semen quality. Molecular Medicine Reports. 2012;6(3):639-44. https://doi.org/10.3892/mmr.2012.965 .

13. Han B, Cheng T, Zhu H, Yu J, Zhu W-j, Song H-d, et al. Genetic Analysis of 25 Patients with 5α-Reductase Deficiency in the Chinese Population. BioMed Research International. 2020;2020(1):1789514. https://doi.org/10.1155/2020/1789514 .

14. Cooper TG, Noonan E, von Eckardstein S, Auger J, Baker HG, Behre HM, et al. World Health Organization reference values for human semen characteristics. Human reproduction update. 2010;16(3):231-45. https://doi.org/10.1093/humupd/dmp048 .

15. Spaziani M, Carlomagno F, Tarantino C, Angelini F, Vincenzi L, Gianfrilli D. New perspectives in functional hypogonadotropic hypogonadism: beyond late onset hypogonadism. Frontiers in Endocrinology. 2023;14:1184530. https://doi.org/10.3389/fendo.2023.1184530 .

16. Skoracka K, Eder P, Łykowska-Szuber L, Dobrowolska A, Krela-Kaźmierczak I. Diet and nutritional factors in male (in) fertility—underestimated factors. Journal of Clinical Medicine. 2020;9(5):1400. https://doi.org/10.3390/jcm9051400 .

17. Nunes DC, Ribeiro JC, Alves MG, Oliveira PF, Bernardino RL. Male sex hormones, metabolic syndrome, and aquaporins: a triad of players in male (in) fertility. International journal of molecular sciences. 2023;24(3):1960. https://doi.org/10.3390/ijms24031960 .

18. Houston BJ, Riera-Escamilla A, Wyrwoll MJ, Salas-Huetos A, Xavier MJ, Nagirnaja L, et al. A systematic review of the validated monogenic causes of human male infertility: 2020 update and a discussion of emerging gene–disease relationships. Human reproduction update. 2022;28(1):15-29. https://doi.org/10.1093/humupd/dmab030 .

19. Kwon A, Kim H-S. Congenital hypogonadotropic hypogonadism: from clinical characteristics to genetic aspects. Precision and Future Medicine. 2021;5(3):97-105. https://doi.org/10.23838/pfm.2021.00093

20. Sugisawa C, Taniyama M, Sato T, Takahashi Y, Hasegawa T, Narumi S. Biallelic PROKR2 variants and congenital hypogonadotropic hypogonadism: a case report and a literature review. Endocrine journal. 2022;69(7):831-8. https://doi.org/10.1507/endocrj.EJ21-0779 .

21. Jin H, Yan M, Pan C, Liu Z, Sha X, Jiang C, et al. Chronic exposure to polystyrene microplastics induced male reproductive toxicity and decreased testosterone levels via the LH-mediated LHR/cAMP/PKA/StAR pathway. Particle and fiber toxicology. 2022;19(1):13. https://doi.org/10.1186/s12989-022-00453-2 .

22. Batista RL, Mendonca BB. Integrative and analytical review of the 5-alpha-reductase type 2 deficiency worldwide. The application of clinical genetics. 2020:83-96. https://doi.org/10.2147/TACG.S198178 .

23. Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, et al. 'Idiopathic'partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? European journal of endocrinology. 2011;165(4):579-87. https://doi.org/10.1530/EJE-11-0580 .

24. Roychoudhury S, Chakraborty S, Choudhury AP, Das A, Jha NK, Slama P, et al. Environmental factors-induced oxidative stress: Hormonal and molecular pathway disruptions in hypogonadism and erectile dysfunction. Antioxidants. 2021;10(6):837. https://doi.org/10.3390/antiox10060837

25. Lane AR, Hackney AC. Reproductive dysfunction from the stress of exercise training is not gender specific: the "exercise-hypogonadal male condition". Journal of endocrinology and diabetes. 2014;1(2):4. https://doi.org/10.15226/2374-6890/1/2/00108 .

26. Winters SJ, Moore Jr JP, Clark BJ. Leydig cell insufficiency in hypospermatogenesis: a paracrine effect of activin–inhibin signaling? Andrology. 2018;6(2):262-71. https://doi.org/10.1111/andr.12459 .

27. Salvio G, Ciarloni A, Cutini M, Delli Muti N, Finocchi F, Perrone M, et al. Metabolic syndrome and male fertility: beyond heart consequences of a complex cardiometabolic endocrinopathy. International Journal of Molecular Sciences. 2022;23(10):5497. https://doi.org/10.3390/ijms23105497 .

28. Kamar MA, Mohamed TY, Latif AMA, AbdElmodaber AM. Effects of Varicocele on Serum Testosterone Levels and Changes of Testosterone Levels after Varicocelectomy among Infertile Men: A Prospective Controlled Study. The Egyptian Journal of Hospital Medicine. 2021;84(1):1731-8. https://doi.org/10.21608/ejhm.2021.176469 .

29. Xiao Q, Wang L, Supekar S, Shen T, Liu H, Ye F, et al. Structure of human steroid 5α-reductase 2 with the anti-androgen drug finasteride. Nature Communications. 2020;11(1):5430. https://doi.org/10.1038/s41467-020-19249-z .

30. Kolasa A, Marchlewicz M, Wenda-Różewicka L, Wiszniewska B. DHT deficiency perturbs the integrity of the rat seminiferous epithelium by disrupting tight and adherens junctions. Folia Histochemica et Cytobiologica. 2011;49(1):62-71. https://doi.org/10.5603/FHC.2011.0010 .

31. Suzuki H, Matsushita S, Suzuki K, Yamada G. 5α-Dihydrotestosterone negatively regulates cell proliferation of the periurethral ventral mesenchyme during urethral tube formation in the murine male genital tubercle. Andrology. 2017;5(1):146-52. https://doi.org/10.1111/andr.12241 .

32. Gui B, Song Y, Su Z, Luo F-H, Chen L, Wang X, et al. New insights into 5α-reductase type 2 deficiency based on a multi-center study: regional distribution and genotype–phenotype profiling of SRD5A2 in 190 Chinese patients. Journal of Medical Genetics. 2019;56(10):685-92. https://doi.org/10.1136/jmedgenet-2018-105915 .