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ORIGINAL ARTICLE

Evaluation of serum hyperprolactinemia status among Iraqi infertile males in Diyala province

Luay Qasim Abdulhameed[1]

[1]*University of Diyala, College of Education for Pure Sciences, Department of Biology, Diyala City-32001, Iraq*

Abstract

Background: In recent decades, a common medical condition known as hyperprolactinemia has been discovered. It is one of the endocrine disorders known to influence male infertility and is found in up to 11% of infertile males. *Aim and Objectives:* To investigate the status of hyperprolactinemia in infertile Iraqi men and its effects on other sexual hormones. *Material and Methods:* Forty-seven infertile males were enrolled in this study, along with twenty-five healthy individuals as controls. Prolactin, testosterone, Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) levels were estimated. *Results:* Infertile males' group had higher levels of prolactin, and lower testosterone, FSH and LH levels than healthy group (23.16 ± 13.23 vs 11.73 ± 1.10, 7.91 ± 1.96 vs. 12.01 ± 2.29, 6.20 ± 2.72 vs. 8.35 ± 1.66, 3.28 ± 1.48 vs. 6.43 ± 1.36) respectively. We divided infertile males' group into two subgroups - one with hyperprolactinemia (n=25), (53.19) and another with normoprolactinemia (n=22) (46.81). Study found that the levels of prolactin were significantly higher with significantly decreased levels of testosterone, LH and FSH levels in hyperprolactinemic subgroup as compared to normoprolactinemic subgroup (33.76 ± 9.14 vs 11.12 ± 1.47, 7.11 ± 1.54 vs 8.82 ± 2.01, 5.30 ± 2.42 vs 7.22 ± 2.73, 2.81 ± 1.22 vs 3.82 ± 1.59) respectively. Additionally, prolactin and FSH were found to be significantly inversely correlated ($r = -0.494$; $p < 0.05$). *Conclusion:* Our study showed that hyperprolactinemia in infertile males had a considerably unfavorable impact on the endocrine parameters and were significantly associated with lower levels of testosterone, FSH, and LH.

Keywords: Male infertility, Prolactin, Hyperprolactinemia, Normoprolactinemia

Introduction

Male infertility is becoming more common and concerning around the world, and has a variety of negative effects on the impacted couple [1-2]. Given that over half of all cases of infertility worldwide involve males, understanding its fundamental mechanisms is crucial [3]. Infertility affects around 15-20% of couples after engaging in regular, unprotected intercourse for at least a year [4]. Male infertility can be caused by sperm antibodies, gonadotoxins, neurological disorders, trauma, infections, genetic disorders and endocrinological disorders (hormonal imbalance) [5]. Endocrinological disorders are usually reversible causes of male infertility. Endocrine system plays a vital role in controlling reproductive activities and involves a complicated interplay of hormones for male reproductive system to function [6].

Gonadotropin Releasing Hormone (GnRH), released from hypothalamus, is the primary factor controlling both male and female mammalian reproduction. It induces the pituitary gland to secrete Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) by binding G-protein coupled receptors on gonadotropes [7]. While, LH

indirectly stimulates sperm production by causing testosterone to be synthesized in Leydig cells, FSH directly boosts spermatogenesis by acting on seminiferous tubules in Sertoli cells [8].

Moreover, testosterone is regarded as necessary for the development and generation of sperm, as well as for secondary sexual traits, functions, and anabolic effects. Testosterone stimulates Sertoli cells' Androgen Receptors (AR) to become functional, triggering the responses necessary for spermatogenesis [9].

On the other hand, prolactin secreted by the pituitary gland, controls the synthesis of LH and FSH by regulating the release of GnRH through a feedback mechanism on the hypothalamus [10]. In recent decades, hyperprolactinemia is being detected commonly among the general population worldwide. It is one of the endocrine disorders known to influence male infertility and is found in up to 11% of infertile males [11]. Numerous studies have confirmed that hyperprolactinemia, one of the reversible causes of infertility, plays a significant role in male infertility [12]. According to studies, undetected subtle abnormal levels of prolactin may be related in a significant number of cases of undiagnosed male infertility [11]. Therefore, our study aimed to investigate the status of hyperprolactinemia in Iraqi infertile males and its effects on other sexual hormones.

Material and Methods

Subjects

Forty-seven infertile males were enrolled in this study. After confirming their abnormal semen findings, they were asked to abstain from sexual activity for three days before the test, and then present for hormonal evaluation.

Along with cases, twenty-five healthy individuals were recruited as controls. Samples were collected from all participants during the time period of September 15, 2021 to August 20, 2022.

Ethical approval

The study was approved by the Council College of Education for Pure Sciences/University of Diyala's local ethics committee (Code: CEPS.UD.REC NO.190.16/11/2023).

Inclusion and Exclusion criteria

Male participants in the reproductive age group were chosen based on their medical and dietary histories. Patients with a history of urogenital issues, sexually transmitted diseases, or any other severe chronic illnesses that might affect the reproductive system were excluded. Patients who had a history of taking medications for a particular disorder or supplementing with antioxidants that could affect the quality of their sperms were also excluded.

Collection of samples and laboratory procedures

The samples were collected from infertile males and healthy controls, aged 29-46 years, hailing from different regions of Diyala Province, and were sent to consulting clinics and specialized laboratories in Baqubah city/ Diyala Province, Iraq, for the purpose of diagnosis and treatment. All participants were recruited after taking written informed consent. Height and weight were measured to calculate their Body Mass Index (BMI) using the formula BMI = Weight (kg) / Height $(m)^2$ [13].

Six ml of venous blood were drawn from both groups, and then placed in a special tube. Once the

blood coagulated, serum was extracted from the clotted blood cells using centrifuge at 5000 rpm for ten minutes following which it was kept in Eppendorf tubes at -20°C. Enzyme-linked immunosorbent assay (ELISA) (kits from Sunlong Biotech, China) was used to measure the serum levels of prolactin, testosterone, FSH and LH.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 17.01 was used for the statistical analysis to evaluate differences in parameters. Pearson correlation and independent samples t-test were used to assess strength of association and comparing means, respectively while mean and standard deviation were calculated to compare group parameters. The threshold for statistical significance was set at $p < 0.01$ or 0.05.

Results

The results in Table 1 show that both groups' ages were comparable ($p < 0.05$). Whereas, there was no difference in BMI between the two groups ($p = 0.212$). In the same table, difference between the mean serum levels of prolactin ($p < 0.001$) in the infertile group compared to healthy group (23.16 ± 13.23 vs11.73 ± 1.10) was highly significant. While the infertile group's mean serum levels of testosterone, FSH, and LH were lower than those of the healthy group. ($p < 0.001$), (7.91 ± 1.96 vs. 12.01 ± 2.29, 6.20 ± 2.72 vs. 8.35 ± 1.66, 3.28 ± 1.48 vs. 6.43 ± 1.36) respectively.

Table 2 shows that [14], hyperprolactinemia was observed in 53.19% (n = 25) of infertile males, while normoprolactinemia was observed in 46.81% (n = 22) ($p < 0.001$).

Table 1: Comparison of study variables among infertile males and healthy controls

Variables	Infertile males Mean ± SD (n=47)	Healthy controls Mean ± SD (n=25)	*p*
Age (years)	34.36 ± 4.15	32.28 ± 2.13	<0.05*
BMI (kg/m^2)	22.32 ± 3.62	21.26 ± 2.95	0.212 NS
Prolactin (ng/ml)	23.16 ± 13.23	11.73 ± 1.10	<0.001**
Testosterone (nmol/L)	7.91 ± 1.96	12.01 ± 2.29	<0.001**
FSH (ng/ml)	6.20 ± 2.72	8.35 ± 1.66	<0.001**
LH (ng/ml)	3.28 ± 1.48	6.43 ± 1.36	<0.001**

*NS: Non-significant, ** p < 0.01, * p < 0.05*
BMI: Body Mass Index, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone

Table 2: Status of serum prolactin in the group of infertile men (n=47)

Serum prolactin status	Level of serum prolactin	n (%)	*p*
Hyperprolactinemia	>13.1 ng/mL	25 (53.19)	<0.001**
Normoprolactinemia	<13.1 ng/mL	22 (46.81)	

*** p < 0.01*

Table 3 shows study variables comparison based on the level of serum prolactin. According to the study's findings, there were no significant differences in age and BMI between people with hyperprolactinemia and those with normoprolactinemia ($p = 0.731$, $p = 0.558$) respectively. While, there were highly significant differences ($p < 0.001$) between the mean serum levels of prolactin in hyperprolactinemia compared to normoprolactinemia (33.76 ± 9.14 vs 11.12 ± 1.47). Additionally, there were significantly lower mean serum levels of testosterone, FSH, and LH ($p < 0.001$) in hyperprolactinemia group compared to normoprolactinemia group (7.11 ± 1.54 vs 8.82 ± 2.01, 5.30 ± 2.42 vs 7.22 ± 2.73, 2.81 ± 1.22 vs 3.82 ± 1.59) respectively.

As shown in Table 4, serum prolactin and FSH were shown to be significantly inversely correlated (r = -0.494; $p < 0.05$). On the other hand, non-significant inverse correlation was found between serum prolactin and testosterone and LH (r = -0.218; $p = 0.295$, r = -0.377; $p = 0.064$) respectively.

Table 3: Comparing the study variables based on the level of serum prolactin

Variables	Hyperprolactinemia Mean ± SD n=25	Normoprolactinemia Mean ± SD n=22	*p*
Age (years)	34.56 ± 4.46	34.13 ± 3.85	0.731 NS
BMI (kg/m^2)	22.03 ± 3.21	22.66 ± 4.08	0.558 NS
Prolactin (ng/ml)	33.76 ± 9.14	11.12 ± 1.47	<0.001**
Testosterone (nmol/L)	7.11 ± 1.54	8.82 ± 2.01	<0.001**
FSH (ng/ml)	5.30 ± 2.42	7.22 ± 2.73	<0.001**
LH (ng/ml)	2.81 ± 1.22	3.82 ± 1.59	<0.001**

*NS: Non-significant, ** p < 0.01*
BMI: Body Mass Index, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone

Table 4: Correlation between prolactin level with study variables in hyperprolactinemia group (n=25)

Prolactin (ng/ml)	Testosterone (nmol/L)	FSH (ng/ml)	LH (ng/ml)
Pearson Correlation	-0.218	-0.494	-0.377
Sig	*0.295 NS*	*<0.05**	*0.064 NS*

*NS: Non-significant, * $p < 0.05$*
BMI: Body Mass Index, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone

Discussion

This study revealed increased levels of hyperprolactinemia with significantly reduced serum levels of FSH, LH and testosterone among infertile males as to compared to the healthy controls ($p<$ 0.001). This is in line with other earlier studies that found higher blood prolactin level being associated with infertility, impotence, hypogonadism, and galactorrhea. On the other hand, according to previous studies, people with asthenozoospermia tend to have lower or higher serum prolactin levels, which may affect sperm motility [15]. The mechanism by which elevated serum prolactin causes poor spermatogenesis in healthy men is unknown [16]. According to a study, prolactin blocks pulsatile GnRH secretion, which then blocks the pulsatile release of LH, FSH and testosterone, thereby significantly impacting spermatogenesis. As a result, males may present with hypogonadism or infertility, which can range from sperm quality changes to complete spermatogenic arrest [17]. Recent research suggests prolactin receptors have been found in Sertoli cells, Leydig cells, and epithelial cells of efferent ducts, indicating prolactin may play a role in promoting steroidogenesis and spermatogenesis, thereby directly impacting male fertility. [18-19].

In the present study, mean serum testosterone, FSH, LH levels were significantly lower in infertile group than the healthy group, comparable to other researchers' findings [10, 20-21]. According to recent research, lack of LH and FSH prevents the gonads from making enough high-quality testosterone or sperm. [22]. Thus, if pituitary fails to secrete LH and FSH, testicular function will be disrupted resulting in infertility [23]. Interestingly, FSH plays a key role in stimulating mitotic and meiotic DNA synthesis in spermatogonia. Whereas LH indirectly promotes spermatogenesis by stimulating the Leydig cells to produce testosterone, which then works in conjunction with FSH to regulate the creation of spermatogonial cells and spermatogenesis in the Sertoli cells [24-25].

As compared to normoprolactinemic subjects, the current investigation found a higher frequency of hyperprolactinemia, which was consistent with other study [26]. The disparities between the reported frequencies could be attributable to the variations between the studies, including population characteristics, measurement techniques, and diagnostic metrics used to define hyperprolactinemia.

The results of the present study confirmed that hormonal levels were reduced significantly in the hyperprolactinemia group as compared with the normoprolactinemia group, while prolactin levels were found to be significantly elevated in hyperprolactinemia group compared with the normoprolactinemia group ($p < 0.001$). Hyperprolactinemia inhibits the pulsatile secretion of the GnRH, which results in a decrease in the pulsatile release of the hormones LH, FSH and testosterone. This, in turn, results in arrest of spermatogenesis, altered sperm quality and impaired sperm mobility. It subsequently results in secondary hypogonadism and infertility [27]. According to a different study, acute hyperprolactinemia can suppress testosterone production and male fertility by either increasing the secretion of adrenal corticoids in response to hypersecretion of prolactin or by inhibiting the secretion of GnRH by prolactin receptors on hypothalamic dopaminergic neurons [28].

In our study, serum prolactin was inversely correlated with all hormones. Also, there was significant correlation between prolactin and FSH ($p < 0.05$). Hyperprolactinemia leads to hypogonadism which in turn reduces gonadal steroid secretion, which modifies positive feedback effects on the hypothalamus and pituitary leading to lack of gonadotropin cyclicity (LH and FSH levels decline) and infertility. Thus, these findings support the elevation of prolactin in our study, but the normal levels of FSH and LH did not alter significantly in the presence of elevated prolactin levels [29]. Furthermore, that high seminal prolactin levels have also been found to negatively impact the functional capacity of sperm [30]. Studies looking at the testicular histopathology of infertile men with hyperprolactinaemia found that spermatogenesis was impaired to varying degrees, ranging from hypospermatogenesis to complete absence of all germ cells [11]. Several restrictions in this study must be acknowledged. First, a limited sample size may limit the generalizability of the results. Second, the study was limited to infertile male Iraqis hailing from Diyala Province only. As a result, when interpreting the results, care should be taken. Furthermore, the study relied on self-reported data, which may be vulnerable to recall bias. More research with bigger sample sizes and various groups is needed to validate the findings and examine the results' generalizability.

Conclusion

An important aspect of evaluating male infertility is hormone measurement. Prolactin is a key player and has a significant impact on the pathophysiology of male infertility, potentially changing the testicular function and semen production. This study showed a greater prevalence of hyperprolactinemia as compared to prior studies. Additionally, evaluations of endocrine markers showed that hyperprolactinemia in infertile males had considerably unfavorable impact on the on endocrine parameters. As grades and the severity of hyperprolactinemia worsened in the infertile group relative to the healthy group, there was an associated significant reduction in the mean serum levels of testosterone, LH and FSH. This study suggests that current protocols should include evaluation and measurement of prolactin during male infertility assessment.

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Author for Correspondence:
Dr. Luay Qasim Abdulhameed, University of Diyala, College of Education for Pure Sciences, Department of Biology, Diyala City-32001, Iraq
Email: biology.man1986@gmail.com
Cell: +9647716676800

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