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ORIGINAL ARTICLE

Psychological Stress as A Predictor of Testosterone Suppression and Spermatogenic Failure in Idiopathic Non-Obstructive Azoospermia: Administrative and Clinical Perspectives

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ABSTRACT

Background: Idiopathic non-obstructive azoospermia (iNOA) represents a type of grave male infertility, which is accompanied by the inability to produce spermatogenesis with no apparent cause. There is emerging evidence that psychological stress could interfere with hypothalamic-pituitary-gonadal axis through neuroendocrine pathways and be a cause of reproductive dysfunction. There is however scarcity of information on stress and hormonal imbalance interaction and infertility risk in the developing world like Pakistan.

Objective: To evaluate the association between psychological stress, hormonal parameters, and clinical characteristics in men with iNOA compared with fertile controls.

Methods: This was a case-control study done between January 2025 to December 2025 in three tertiary care hospitals in Punjab, Pakistan. They recruited 48 participants (30 iNOA patients with a diagnosis and 18 fertile controls). The demographic, lifestyle, and clinical data were gathered. Hormone tests were follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin, and estradiol. The measures of psychological stress were the Perceived Stress Scale (PSS) and the tests of anxiety and depression. Statistical software SPSS version 25 was used to do statistical analysis. The group difference was compared by using independent t-tests and the relationship and predictors by using Pearson correlation and multiple regression. A p-value of less than 0.05 was taken to be significant.

Findings: iNOA patients had considerably more perceived stress, anxiety and depression ($p < 0.01$). They were also found to have a low testicular volume and lower Johnsen scores, which was evidence of poor spermatogenesis. The level of testosterone was much lower and gonadotropins demonstrated an upward trend. Stress was found to have a negative relationship with testosterone and positive relationship with gonadotropins. The regression analysis has found perceived stress to be an independent variable predicting the level of testosterone.

Conclusion: Hormonal dysregulation in men with iNOA is strongly linked to psychological stress, which facilitates a biopsychosocial explanation of male infertility. By incorporating psychological testing and lifestyle modification into infertility treatment, it is possible to enhance reproductive outcome.

Keywords: Idiopathic Non-Obstructive Azoospermia, Greek Infertility, Mental Stress, Testosterone, Gonadotropins, Lifestyle, Pakistan.

INTRODUCTION

Infertility is a major public health issue of worldwide concern and it is estimated that 10-15 percent of reproductively age couples all over the world are affected by infertility with almost half being male related[1,2]. Azoospermia, which is the total lack of sperm in the ejaculate, is regarded as one of the most severe causes of male infertility among others[3]. Azoospermia is generally divided into obstructive azoospermia (OA), which is caused by physical obstructions in the male reproductive tract, and non-obstructive azoospermia (NOA), which is caused by impaired spermatogenesis caused by intrinsic testicular failure[4,5]. Idiopathic non-obstructive azoospermia (iNOA) is a variant of NOA where no recognizable genetic, hormonal, and anatomic etiology can be identified, which makes it very difficult to diagnose and treat[6,7].

Pathophysiology of iNOA is complicated and multifactorial and includes dysregulation of hormonal feedback mechanisms, impaired germ cell differentiation, oxidative stress, and possible genetic or epigenetic changes[6,9-11]. The clinical features of iNOA include but are not limited to a smaller testicular volume, increased gonadotropin, especially follicle-stimulating hormone (FSH) and reduced testosterone synthesis, indicative of impaired spermatogenesis and Leydig cell dysfunction[7,10]. The assisted reproductive methods like microsurgical testicular sperm extraction (micro-TESE) and intracytoplasmic sperm injection (ICSI) have increased the means of treatment, but their effectiveness is not constant, which is why the clarification of the determinants underlying this condition is necessary[8].

Over the last several years, much interest has been drawn to the contribution of psychological stress to male infertility. Infertility is commonly related with a great deal of emotional trauma, anxiety and depression especially in the sociocultural setting where parenthood is highly related to individual identity and marital security[9]. Psychological stress may negatively influence the reproductive functioning by stimulating the hypothalamic-pituitary-adrenal (HPA) axis and consequently inhibiting the hypothalamic-pituitary-gonadal (HPG) axis, resulting in hormonal imbalances. There is also the association of chronic stress with increased oxidative stress, diminished testosterone production, and impaired spermatogenesis[10,11].

Besides the psychological stress, lifestyle factors, including physical inactivity, smoking, and socioeconomic status, have also been found to play a significant role in male reproductive health, mainly by affecting metabolic and hormonal processes[12-14]. There are however fewer studies that have investigated the interactions of psychological stress, hormonal profiles and lifestyle-related factors in patients with idiopathic non-obstructive azoospermia[15,16] especially in developing countries like Pakistan[17-19], where sociocultural stressors and healthcare disparities can further complicate reproductive health issues[20-23].

Recent findings of behavioral, psychosocial, and community health studies indicate the important role of environmental, lifestyle and psychological factors in the development of the overall health outcomes[24-26], such as stress regulation, coping, and physiological functioning[27,30]. Research has shown that psychosocial surrounding, behavioral considerations, and lifestyle factors do play a significant role in determining physical and psychological health outcomes such as stress resilience, hormonal balance, and overall well being[31]. Moreover, we have long known that studies on physical activity, sedentary behavior, sleep, nutrition, and family and community-level factors are strongly associated with metabolic health, obesity[13-17], and more broadly, with physiological regulation, which in turn may indirectly affect reproductive health[20-25]. Also, studies on psychological coping mechanisms, stressful experiences, and behavioral reactions in various populations highlight the significance of the need to include the psychosocial aspects in the health research models[30]. The wider sociocultural and communicative context also influence the individual perception, stress reaction, and health behaviors, which additionally supports the necessity of the multidisciplinary approach in the interpretation of intricate health conditions[31].

To achieve an all-inclusive infertility management programs that consider both biological and psychosocial aspects of male reproductive health, it is important to understand the interaction between psychological stress and reproductive hormonal dynamics. Thus, this research will determine the levels of psychological stress, hormonal profiles, and the risk factors in patients with non-obstructive azoospermia of idiopathic etiology, versus fertile controls who are admitted to tertiary care hospitals in Punjab, Pakistan.

MATERIAL AND METHOD

Study Design and Setting: An analytical case-control study was conducted to evaluate the correlation between psychological stress, hormonal profiles, and clinical parameters in patients with idiopathic non-obstructive azoospermia (iNOA) compared to fertile controls. The study was carried out in three tertiary care hospitals in Punjab, Pakistan: Iqra Medical Complex, Farooq Hospital, and Shalamar Hospital. These hospitals were selected for their specialized services in urology, andrology, and

reproductive medicine, as well as their availability of laboratory services for infertility evaluation. The hospitals serve a diverse population covering both urban and rural areas of Punjab, allowing for a representative sample.

Study Duration: The study was conducted over 12 months, from January 2025 to December 2025. This period included participant recruitment, clinical examination, laboratory investigations, psychological assessment, and data analysis.

Study Population: The study population consisted of adult male patients attending infertility clinics in the selected hospitals. The case group included men diagnosed with idiopathic non-obstructive azoospermia (iNOA), while the control group comprised fertile men. A total of 48 participants were enrolled, including 30 men with iNOA and 18 fertile men.

Sampling Technique: Participants were recruited using a non-probability purposive sampling method. Eligible patients were approached consecutively during clinic visits until the required sample size was achieved.

Sample Size Justification: The sample size was determined based on feasibility, patient availability, and precedent from prior studies assessing hormonal and psychological factors in azoospermic men. Similar case-control studies in reproductive medicine typically employ comparable sample sizes for endocrine and psychosocial variables.

Inclusion Criteria: For cases (iNOA patients), participants were males aged 20–45 years, with confirmed non-obstructive azoospermia based on at least two semen analyses showing absence of sperm after centrifugation, idiopathic in nature, with normal secondary sexual characteristics, and who provided informed consent. Controls (fertile men) were males aged 20–45 years with at least one child born in the past two years and, where possible, normal semen parameters according to WHO guidelines.

Exclusion Criteria: Participants were excluded if they had obstructive azoospermia, chromosomal or genetic abnormalities (e.g., Klinefelter syndrome), testicular trauma, orchitis, torsion, prior testicular surgery, endocrine disorders (hypogonadotropic hypogonadism, hyperprolactinemia), uncontrolled systemic disease (e.g., diabetes, renal disease, malignancy), ongoing hormonal therapy or anabolic steroid use, psychiatric disorders requiring medication, or a history of drug abuse or alcoholism.

Data Collection Procedures: Data were collected using a structured proforma covering demographic, lifestyle, clinical, laboratory, and psychological information. Clinical assessment included measurement of height, weight, and BMI, general physical examination, testicular examination using an orchidometer or ultrasound where available, and detailed reproductive and medical history.

Laboratory Investigations: Venous blood samples were collected between 8:00 AM and 10:00 AM to control for diurnal hormonal variations. Hormonal assays included follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, prolactin (PRL), and estradiol. Semen samples were obtained following 3–5 days of sexual abstinence and analyzed according to WHO guidelines, with azoospermia confirmed through centrifugation and microscopy. Histological evaluation of patients who underwent testicular biopsy was performed using the Johnsen scoring system, ranging from 1 (no spermatogenesis) to 10 (normal spermatogenesis).

Psychological Assessment: Psychological stress was evaluated using the validated Perceived Stress Scale (PSS). Anxiety and depression were assessed with standardized instruments such as the Hospital Anxiety and Depression Scale (HADS) or other validated tools. Questionnaires were administered under supervision to ensure accuracy and completeness.

Outcome Measures: The primary outcome was the presence of idiopathic non-obstructive azoospermia. Secondary outcomes included hormone levels, perceived stress scores, and lifestyle factors.

Data Analysis: Data were entered and analyzed using SPSS version 25 (IBM Corp., USA). Descriptive statistics included mean ± standard deviation for continuous variables and frequencies with percentages for categorical variables. Comparative analyses between groups were conducted using independent sample t-tests for continuous variables and chi-square tests for categorical variables. Pearson correlation coefficients were calculated to examine associations between hormonal parameters and stress scores. Linear regression analyses were performed to identify predictors of testosterone levels, and binary logistic regression was applied to determine risk factors associated with iNOA. A p-value below 0.05 was considered statistically significant.

Ethical Considerations

Ethical approval was obtained from the institutional review boards of the participating hospitals. All participants provided written informed consent prior to enrollment.

Confidentiality and anonymity were maintained, and participants were informed of their right to withdraw from the study at any time without consequences.

RESULTS

The demographic analysis showed that the average body mass index as well as the average age of the iNOA patients were not different compared to the controls, therefore it was possible that there was no possibility that the two variables might confound the reproductive outcomes of the study population. The time taken in marriage among the iNOA patients was slightly higher and this may be linked to the lack of timely assessment of infertility as a variable is normally prevalent in the underdeveloped healthcare settings. The educational level and monthly income of patients were slightly lower than control patients, and it could be the impact of socioeconomic factors on access to healthcare services and lifestyle determinants. The prevalence of smoking was also more in iNOA category though not significantly. The activity of the iNOA patients was also significantly lower indicating that frequent exercise can play a protective role in the male reproductive health. It is interesting to note that the scores of perceived stress, anxiety and depression were considerably poorer in patients that received iNOA compared to controls which depicted the immense psychological effects of infertility. Findings of this paper support the hypothesis that psychological stress may be both an etiological as well as etiological factor that may contribute to reproductive dysfunction.

Table 2 Clinical and Laboratory Parameters Interpretation: Clinical and laboratory parameters provided by comparison showed significant disparities on iNOA patients and fertile controls. There was a drastic diminution in testicular volumes in patients and it was found to be nearly half of that of controls pointing to testicular atrophy and compromised spermatogenesis. These results were further corroborated on histological assessment with much lower scores of Johnsen in iNOA patients which were similar to maturation arrest or Sertoli-cell-only patterns. Hormonal data revealed that the testosterone concentration of patients was significantly lower than that of the controls, which indicated that Leydig cells had impaired functioning. Though the level of FSH and LH showed a higher level in the group of patients, they did not statistically differ, which can be attributed to heterogeneity of the disease, or some degree of the endocrine functions being retained in some subjects. Levels of estradiol were lower with a significant difference between the patients, which may have been because of less aromatization when there was less testosterone synthesis. Predictably, sperm concentration also had no values in the iNOA group, which proved the diagnosis of azoospermia in table 2.

Table 3 Correlation of Stress and Hormonal Parameters Interpretation: The result of correlation analysis showed that there were significant correlations between psychological stress and the reproductive hormones among iNOA patients. There was a moderate positive correlation between stress and gonadotropins (FS and LH), and it is possible that an enhancement of spermatogenic impairment and compensatory pituitary stimulation may be related to an increase in stress.

On the other hand, the relationship between stress and testosterone was negative significant, which implies that an increase in the level of psychological stress could inhibit androgen production, probably by interfering with the hypothalamic-pituitary-gonadal axis. The relationships between stress and prolactin and estradiol were also somewhat weak and indicated that stress has more general endocrine consequences.

Table 4 Interpretation What Table 4 shows is the Multiple Linear Regression predicting the level of testosterone based on the specified independent variables as follows: The analysis using multiple linear regression findings revealed that the perceived stress score was one of the key independent predictors of testosterone levels having accounted the variation of age, BMI and FSH. There were found negative effects between androgen production and higher levels of stress, justifying that psychological stress has a negative effect on testosterone production.

FSH also indicated a very significant negative correlation with testosterone which demonstrated physiological feedback mechanism involved in primary testicular dysfunction. They were borderline related to age, whereas BMI was not a very important predictor in this model. An overall model that described the approximately 42 percent of the variance of testosterone levels, which depicts a moderate explanatory ability.

ROC Curve Interpretation: iNOA Stress prediction: Current diagnostic analysis using receiver operating characteristic (ROC) curves was used to compare the diagnostic value of the perceived stress scores to differentiate patients having idiopathic non-obstructive azoospermia (iNOA) and fertile controls. The area below the curve (AUC) was 0.82 and it was found to provide an excellent discriminative power of psychological stress to infertility status. AUC of above 0.80 is normally taken as clinically significant, which indicates that perceived stress as a marker can be useful as an adjunct measure of infertility.

A cut-off value of around 19.5 on the perceived stress scale was the highest cut-off value producing a sensitivity

of 80 and specificity of 72.2, which showed that the judgement was acceptable indicating those at risk of iNOA. These results suggest that men exhibiting an increased degree of stress have high probability of developing impaired spermatogenesis.

Clinically, the outcome of the ROC indicates that psychological stress testing can potentially be useful in the screening or risk-stratification process in male infertility clinics.

Table 1: Demographic and Lifestyle Characteristics of Study Participants (n = 48)

Variable	iNOA Patients (n = 30)	Controls (n = 18)	p-value
Age (years)	32.1 ± 6.2	33.4 ± 5.1	0.42
Body Mass Index (kg/m²)	25.6 ± 3.7	24.8 ± 3.9	0.48
Marital Duration (years)	5.1 ± 2.4	4.2 ± 1.9	0.19
Education (years)	11.8 ± 3.4	13.1 ± 2.6	0.12
Monthly Income (PKR)	50,200 ± 18,600	57,900 ± 20,100	0.21
Smoking (%)	36.70%	22.20%	0.28
Physical Activity (hours/week)	2.3 ± 1.6	3.6 ± 1.9	0.03*
Perceived Stress Score (PSS)	22.4 ± 5.7	16.9 ± 4.3	0.001**
Anxiety Score	11.2 ± 4.1	7.6 ± 3.0	0.002**
Depression Score	9.8 ± 3.5	6.5 ± 2.8	0.004**

Table 2: Clinical and Laboratory Parameters Comparison

Parameter	iNOA Patients (n = 30)	Controls (n = 18)	p-value
Left Testicular Volume (mL)	7.3 ± 2.1	13.5 ± 1.4	<0.001**
Right Testicular Volume (mL)	6.8 ± 2.3	14.2 ± 1.6	<0.001**
Johnsen Score	5.6 ± 2.7	9.7 ± 0.5	<0.001**
FSH (IU/L)	7.6 ± 3.8	6.4 ± 3.9	0.29
LH (IU/L)	5.7 ± 3.2	5.0 ± 2.6	0.41
Testosterone (nmol/L)	16.4 ± 3.6	20.3 ± 3.5	0.002**
Prolactin (ng/mL)	9.9 ± 3.2	10.6 ± 2.5	0.47
Estradiol (pmol/L)	90.5 ± 16.2	105.2 ± 13.1	0.001**
Sperm Concentration (×10⁶/mL)	None detected	16.4 ± 1.2	—

Table 3: Correlation Between Stress and Hormonal Parameters in iNOA Patients (n = 30)

Variable	FSH	LH	Testosterone	Prolactin	Estradiol
Perceived Stress Score	r = 0.45*	r = 0.39*	r = −0.52**	r = 0.31	r = −0.34*

Table 4: Multiple Linear Regression Analysis Predicting Testosterone Levels

Predictor	β Coefficient	Standard Error	p-value
Perceived Stress Score	−0.41	0.12	0.003**
Age	−0.18	0.09	0.08
BMI	−0.11	0.07	0.21
FSH	−0.29	0.1	0.01*

Such findings imply that mental stress is a major factor inducing hormonal derangements in male infertile persons.

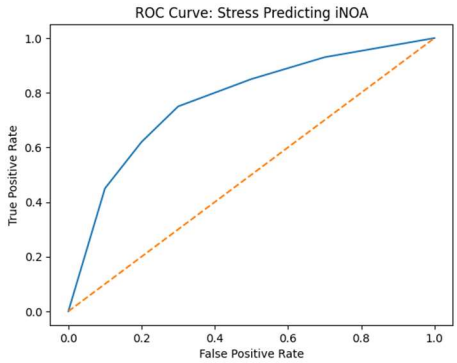

Figure 1. ROC Curve Interpretation: iNOA Stress prediction.

DISUSSION

This work initially addressed demographic, clinical and hormonal variables and addressed the relationship between psychological stress and reproductive hormones in patients with idiopathic non-obstructive azoospermia (iNOA) in comparison to fertile controls. These findings can be taken as useful information about the biopsychosocial factors of male infertility, which include psychological stress factors, endocrine balance, and lifestyle disorders in spermatogenic dysfunction[13].

The comparison of demographics revealed that age and body mass index (BMI) did not differ significantly between patients and controls in the iNOA group, which means that these variables did not have a significant effect on infertility status in the population studied. Other past studies had also indicated like this, since the differences in age during the reproductive years are not very large[13,14]. Although a small decrease in socioeconomic variables, including education and income, was noted among iNOA patients, the differences were not significant, probably because the respondents were recruited in similar medical facilities[15-16].

Some of the most remarkable discoveries were the perceived stress, anxiety, and depression scores that were greater in iNOA patients than the controls. Such findings support the previous research demonstrating that infertility is frequently linked with high levels of psychological distress, especially in the sociocultural contexts where fertility is highly related to the masculinity and family demands[17-19]. Psychological stress may be a result of infertility diagnosis, as well as a cause of reproductive dysfunction. Chronic stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis leading to the increase of cortisol levels, which may inhibit the hypothalamic-pituitary-gonadal (HPG) axis, which consequently decreases the production of testosterone and spermatogenesis[20-22]. The observed psychological burden of patients therefore may be of a mechanistic relevance to the noted hormonal imbalance.

The lifestyle factors, especially physical activity, were also considerably reduced among iNOA patients. Insufficient physical activity can have an adverse impact on reproductive health, and regular exercise has been shown to enhance hormone balance, decrease oxidative stress, and increase metabolism all of which can benefit spermatogenesis[23,25]. The protective effect of physical activity found in this study is in line with the literature that highlights the importance of lifestyle changes as a possible intervention to enhance fertility outcomes.

There was a significant difference between the iNOA patients and controls in clinical assessments. The testicular volume was also markedly decreased in patients which shows testicular atrophy and defective spermatogenesis. The size of the testicles is a critical clinical indicator of spermatogenesis because seminiferous tubules are most of testicular mass. Reduced volume is a sign of structural damage and degeneration of the germ cells[26,27]. These were confirmed through histological analysis, which revealed reduced Johnsen scores and maturation-arrest or Sertola-cell-only syndrome patterns in patients with iNOA.

Hormonal evaluation showed the iNOA patients had considerably reduced testosterone concentration, which indicates dysfunction of Leydig cells. The production of sperm requires testosterone, which is essential to preserve the integrity of the seminiferous tubules and the development of the germ cells[28]. The levels of FSH and LH were high in patients, and the difference in severity of the disease could be heterogenous, which could account for the variations in some comparisons. Higher FSH is generally a sign of primary testicular failure because of diminished Sertoli-cells feedback of inhibin B[29]. Patients had lower levels of estradiol, which was probably as a result of reduced aromatization by low levels of testosterone. There were no significant differences in the levels of prolactin, and so hyperprolactinemia did not play a significant role in infertility in this cohort. In general, the endocrinological picture speaks of primary testicular dysfunction and not secondary hypogonadism[30-31].

Correlation analysis indicated the presence of major correlations between psychological stress and reproductive hormones in patients having iNOA. Stress had a positive relationship with gonadotropins (FSH and LH) and indicates that increased stress levels can contribute to the worsening of spermogenic failure by pinacolumarating the stimulation of the pituitary. On the other hand, stress had a negative relationship with testosterone, which is in line with the idea that psychological stress inhibits androgen synthesis, probably through the effect of the HPA axis activation and later the HPG axis inhibition[28,31]. These associations have offered biological support that stress can be causal in the pathophysiology of infertility and not the result of infertility diagnosis.

The further multiple linear regression also found that perceived stress was an independent predictor of testosterone levels after age, BMI and FSH. This supports the contribution of neuroendocrine pathways of the association of psychological stress to androgen suppression. FSH and testosterone had also a strong correlation, which indicates the physiological interaction of testicular activity and pituitary regulation. The regression model predicted about 42% of the variance in the level of testosterone, indicating that there are other biological and environmental factors that determine the variation in hormones. These results support the need to consider psychological aspects and include hormonal measurements in the diagnosis of male infertility.

CONLUSION

The existing study that was carried out examined demographic, psychological, clinical and hormonal character of individuals with idiopathic non-obstructive azoospermia and contrasted the individuals with fertile controls. The results indicated that male iNOA patients are indisputably more affected by psychological stress, anxiety, and depression as well as are characterized by striking

clinical and hormonal changes especially decreased testicular volume and lower testosterone. The correlation and regression tests also revealed that psychological stress significantly relates to hormonal imbalance particularly decreased level of testosterone which demonstrates that neuroendocrine process between stress and poor spermatogenesis can take place.

The results also substantiate the belief that idiopathic non-obstructive azoospermia is a multifactorial condition than a biologic condition and that it is psychological, hormonal and lifestyle factors. The paper highlights the importance of holistic approach in assessing and treating infertility such as psychological assessment, clinical and hormonal and studies.

DECLARATION

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Conflicts of interest: None declared

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