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Association Between Stress Hormones and Sperm DNA Fragmentation in Men with Unexplained Infertility

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Abstract

Background: Psychological and physiological stress has been an emerging interest as a likely contributor to male infertility by influencing endocrine regulation and sperm quality. Hormonal changes due to stress may induce a background of oxidative damage that could influence sperm DNA damage and thus affect fertility potential. **Purpose**: The purpose of this study was to explore the relationship between stress hormones and sperm DNA fragmentation in men with idiopathic infertility. **Methods**: A case–control study of 120 men aged 20–45. The subject group consisted of 60 men with unexplained infertility and 60 healthy fertile men as controls. Overnight fasting venous blood samples were taken for the measurement of serum cortisol (µg/dL), adrenocorticotropic hormone (ACTH; pg/mL) and dehydroepiandrosterone (DHEA; µg/dL) by enzyme-linked immunosorbent assay ELISA. Semen was collected from the infertile participants, who they were analyzed by using the staining method (Toluidin Blue TB). **Results**: Serum cortisol (20.84 ± 4.92 vs 16.73 ± 3.85 µg/dL; P = 0.004) and ACTH levels (42.61 ±8.34 vs 34-18±6-79 pg/mL; P =0-002) were significantly higher in the infertile men than healthy controls, respectively In contrast, levels of DHEA were significantly lower in infertile men than those of fertile ones (178.45 ± 38.72 vs. 221.36 ± 42.15 µg/dL; P =0.005). Cortisol (23.41 ± 4.83 vs. 18.47 ± 3.95 µg/dL; P = 0.006) and ACTH levels (46.28 ± 7.91 vs.39,15±6,84

pg/mL;P=0,007) were significantly elevated in men with damaged sperm DNA compared to those without impaired DNA integrity among infertile men. **Conclusions**: Unexplained infertile men have demonstrable evidence for stress-induced endocrine dysfunction characterized by elevated cortisol (and ACTH) levels combined with low DHEA concentrations.

Keywords: Cortisol, DHEA, ACTH, DNA fragmentation, Unexplained Infertility

Introduction

Up to 30-40% of male infertility cases fall under unexplained infertility, where semen parameters appear normal according to clinical lab reports but fertilization failure still occurs (Agarwal et al., 2019). The past years have seen an escalating focus on molecular and functional sperm defects — and in particular sperm DNA fragmentation (SDF) — as mediators of male reproductive potential. SDF has been linked to impaired fertilization, embryo development, reduced rates of clinical pregnancy and live births by ART. Additional pathophysiological mechanisms may be associated with idiopathic infertility where conventional semen analysis can be normal yet the level of sperm DNA damage is already high (Simon et al., 2017).

Another newly emerging aspect of male reproductive dysfunction is the impact of stress-induced endocrine pathways that reflect itself especially to the hypothalamic–pituitary–adrenal (HPA) axis. The axis is activated during psychological and physiological stress, resulting in elevated levels of cortisol and adrenocorticotropic hormone (ACTH) along with changes in dehydroepiandrosterone (DHEA). Cortisol, the primary hormone of the glucocorticoid family which serves as an essential factor in helping adapt to stress, leads to compromised spermatogenesis when expressed chronically and at an elevated level (Whirledge & Cidlowski, 2013) due to its association with oxidative stress, immune dysregulation or endocrine complex imbalance. Corticotropin (ACTH) is a pituitary-derived peptide hormone, which stimulates adrenal synthesis of cortisol and acts as an upstream marker of HPA axis activation. DHEA is a precursor of adrenal androgens, with both protective antioxidant and putative anti-glucocorticoid properties, whose declines in relation to cortisol are viewed as an index of chronic stress burden (Kamin & Korte, 2017).

Accumulating evidence indicates that an alteration in patterns of stress hormones may cause oxidative stress to decrease males' reproductive functions, leading to male infertility. High levels of cortisol decrease testosterone production, affect Sertoli cell function and induce germ cell apoptosis, leading to low sperm quality (Almeida et al., 2020). Furthermore, oxidative stress has proven to be a well-known risk factor for sperm DNA fragmentation since reactive oxygen species (ROS) are directly harmful as the antioxidant defense in sperm is limited and its chromatin tightly packed. An increase in ROS production surpasses the capacity of endogenous antioxidant systems and is associated with single- and double-strand DNA breaks, which are highly negatively correlated with the severity of infertility (Aitken & Krausz, 2016).

In reproductive physiology, ACTH is less well studied but nevertheless indicative of chronic HPA activation with potential indirect contribution to gonadal dysfunction through prolonged elevation of cortisol levels. Maintenance of HPA activation has also been associated with suppression in gonadotropin-releasing hormone (GnRH), marked by a decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release, which are required for proper spermatogenesis to occur [14]. Concomitantly, it has been argued that DHEA opposes the actions of cortisol by acting as an antioxidant and enhancing androgenic pathways. Stressed males have also been observed to have DEHA levels lower than that of cortisol with poor sperm parameters or excessive reproductive malfunction (Turner et al., 2018).

Results: Sperm DNA fragmentation is a newer, more sensitive biomarker of male fertility potential than traditional semen parameters. In clinical studies, increased SDF has been linked to impaired natural conception and poor success rates in IVF and ICSI cycles (Simon et al., 2017). SDF has a complicated etiology that includes oxidative stress, apoptosis, lifestyle factors (obesity/smoking/psychosocial stress), and environmental toxins. Of these, stress-mediated hormonal imbalance is increasingly perceived to be a modifiable risk factor.

While the role of stress in reproductive dysfunction is increasingly recognized, few studies have specifically investigated a combined relationship between cortisol, ACTH and DHEA, and sperm DNA integrity in men with unexplained infertility. This relationship is key in finding potential endocrine biomarkers and therapeutic targets. Examining the stress hormone profiles associated with SDF may elucidate the underlying pathophysiology of idiopathic male infertility and facilitate therapeutic approaches utilizing stress-modulating or antioxidant-based interventions.

Thus, this study evaluates the relationship between stress hormones (cortisol, ACTH and DHEA) and sperm DNA fragmentation in men with unexplained infertility. This relationship is still not clear and examination of this interaction

may lead, in the future, towards better diagnostic approaches and a broader view on male endocrine–reproductive axis disturbance as part of the pathology of idiopathic infertility.

Methods

This case-control descriptive study was conducted at The Fertility Center in Al-Sadr Medical City in Naja city in Iraq. A total of 60 men diagnosed with unexplained infertility were defined as the study population (patient group) and another set of 60 healthy fertile men served as a control group.

Unexplained male infertility is defined as inability to conceive after 12 months of regular unprotected sexual intercourse without evidence of female infertility and no identifiable cause of infertility after routine clinical, hormonal and semen evaluation. The control group consisted of healthy fertile men who had fathered at least one child naturally in the previous two years and did not have a history of infertility.

Inclusion and Exclusion Criteria

In the patient group, men with an unexplained infertility were selected. Patients with identifiable causes of infertility, including varicocele, cryptorchidism, genital tract obstruction, testicular trauma or genetic abnormalities and reproductive tract infections were denied.

Exclusion criteria for both the groups comprised of chronic systemic diseases including diabetes mellitus, hypertension, cardiovascular diseases, chronic renal or hepatic disorders, autoimmune diseases and known endocrine disorders that are affecting adrenal or pituitary function. Patients were also excluded for receipt of corticosteroids, hormonal therapy, psychotropic medications or immunosuppressive agents within the prior three months. The researchers also excluded smokers, alcohol consumers, and subjects with acute illness or febrile episodes in the last 2 weeks before sampling to avoid confounding as the hormonal status and sperm quality vary during these periods.

Ethical Considerations

The institutional ethics committee approved the study protocol. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. All participants provided written informed consent prior to study enrollment.

Sample Collection and Processing

To avoid potential circadian variations in hormone secretion, venous blood samples was drawn from all individuals at 8:00–10:00 AM after a overnight fast of 8–10 h. In the 24 hours prior to blood collection, participants were asked to refrain from strenuous physical activity, caffeine-containing drinks and as much psychological stress as possible. Collected ~ 5 mL of venous blood in plain vacutainer tubes. Samples were kept for clotting at room temperature followed by centrifugation at 3000 rpm for 10 minutes. The serum isolated was divided in aliquots and kept frozen at −20°C until hormonal analysis. Also, semen samples were collected by masturbation after 2–7 days of sexual abstinence. Samples were then placed in a 37°C incubator for half an hour to liquefy prior to continuing with further foundation work.

Hormonal Assays

Concentrations of cortisol (µg/dL), adrenocorticotropic hormone (ACTH, pg/mL) and dehydroepiandrosterone (DHEA, µg/dL) were measured in serum using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Samples were analyzed in duplicate and all procedures underwent quality control during the study period.

Testing of DNA Fragmentation: Toluidine Blue Staining

DNA fragmentation of spermatozoa was assessed using the Toluidine Blue (TB) staining procedure as described previously. In short, thin semen smears were made on silane coated slides and left to dry at ambient temperature. Smears were fixed in a fresh 96% ethanol-acetone solution (1:1) at 4 °C for 1 hour, then air-dried. Slides were then hydrolyzed in 0.1 N hydrochloric acid (HCl) at 4°C for 5 minutes, followed by three rinses for two minutes each with distilled water.

Slides were subsequently stained with 0.05% Toluidine Blue solution (in 50% McIlvaine citrate-phosphate buffer; pH 3.5) for 5 minutes at room temperature and rinsed quickly in deionized water. The slides were then examined using light microscope with oil immersion at ×1000 magnification. For each sample, 300 spermatozoa were analyzed from separate microscopic fields. Sperm heads with normal chromatin integrity appear light blue and spermatozoa inflicted damage to their chromatin by DNA fragmentation appear deep violet or purple. The number of spermatozoa with deep violet staining was expressed as a percentage and calculated as the sperm DNA fragmentation index (figure 1).

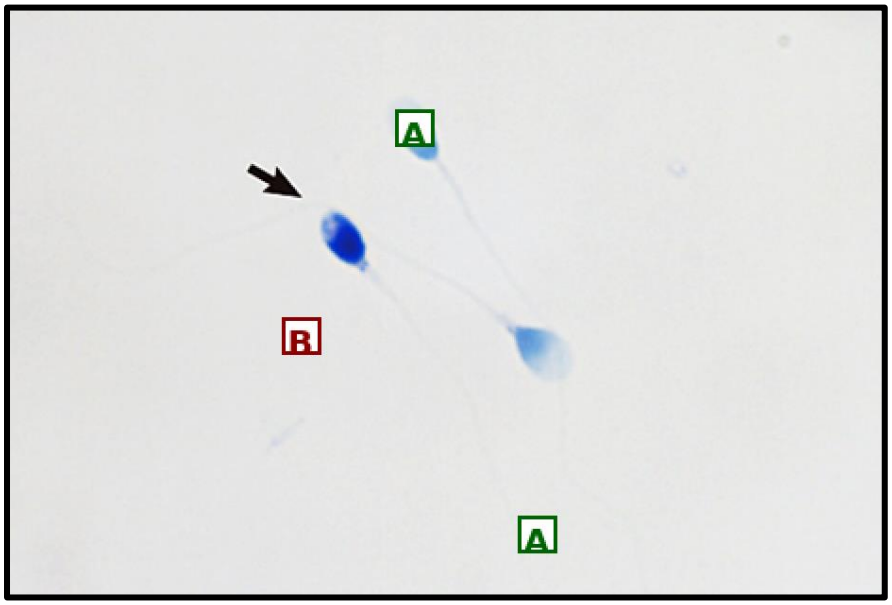

Figure 1. Sperm Cells Stained by Toluidine Blue Staining (TB). A: Normal Sperm Cells with Blue Heads (Intact DNA). B : Abnormal Sperm Cells with purple heads (Damaged DNA)

Statistical Analysis

Statistical analyses were conducted using 26.0 version SPSS software. Quantitative data were presented as mean ± standard deviation (SD). The Shapiro–Wilk test was used to ascertain the normality of data distribution. For normally distributed variables, independent samples t-test was used for comparison of hormonal levels and percentages of sperm DNA fragmentation between infertile patients and healthy controls. Serum cortisol, ACTH and DHEA levels were measured to look for associations with sperm DNA fragmentation between each other, and combined with Pearson's correlation coefficient. Statistical significance was set at $p<0.05$.

The Results

The demographic characteristics of infertile men and healthy controls are shown in Table 1. There were no statistically significant differences between both groups in terms of age distribution (P = 0.412), BMI categories (P = 0.091) and place of residency (P = 0.290). Most of the subjects were between 26 — 30 years old and had normal BMI to overweight. Both groups were more often urban rather than rural residents.

Table 1. Comparison of age, BMI and residence between infertile and healthy men

Items		Patients (N= 60)		Control (N= 60)		(P value)
		Freq.	%	Freq.	%	
Age	16-20	6	10	8	13.3	0.412 (NS)
	21-25	17	28.3	15	25	
	26-30	22	36.7	24	40	
	> 30	15	25	13	21.7	
BMI	Underweight	4	6.7	6	10	0.091 (NS)
	Normal	24	40	29	48.3	
	Overweight	21	35	18	30	
	Obese	11	18.3	7	11.7	
Residence	Urban	38	63.3	34	56.7	0.29 (NS)
	Rural	22	36.7	26	43.3	

*** Non- Significant at P value >0.05**

Stress-related hormone concentrations where significantly different in the infertile men compared to healthy controls and is shown in Table 2. Significantly higher levels of serum cortisol and ACTH than controls were found in infertile (both P = 0.004), suggesting hypothalamic–pituitary–adrenal (HPA) axis activation. In contrast, serum DHEA concentrations were significantly lower in the infertile men than in healthy subjects(P = 0.005). (Table 2).

Table 2. Comparison of levels of hormones between infertile and healthy men

Hormones	Patients (N= 60)		Control (N= 60)		(P value)
	Mean	SD	Mean	SD	
Cortisol (µg/dL)	20.84	4.92	16.73	3.85	0.004 *
ACTH (pg/mL)	42.61	8.34	34.18	6.79	0.002 *
DHEA (µg/dL)	178.45	38.72	221.36	42.15	0.005*

*** High Significant at P value <0.01**

The bar graph, illustrated in figure 2., shows that with a significantly elevated mean level of ASA The presented data reveal a marked elevation in sperm DNA fragmentation (SDF) among infertile patients (48.2%) relative to fertile controls (22.6%), representing a 2.1-fold increase in damaged DNA.

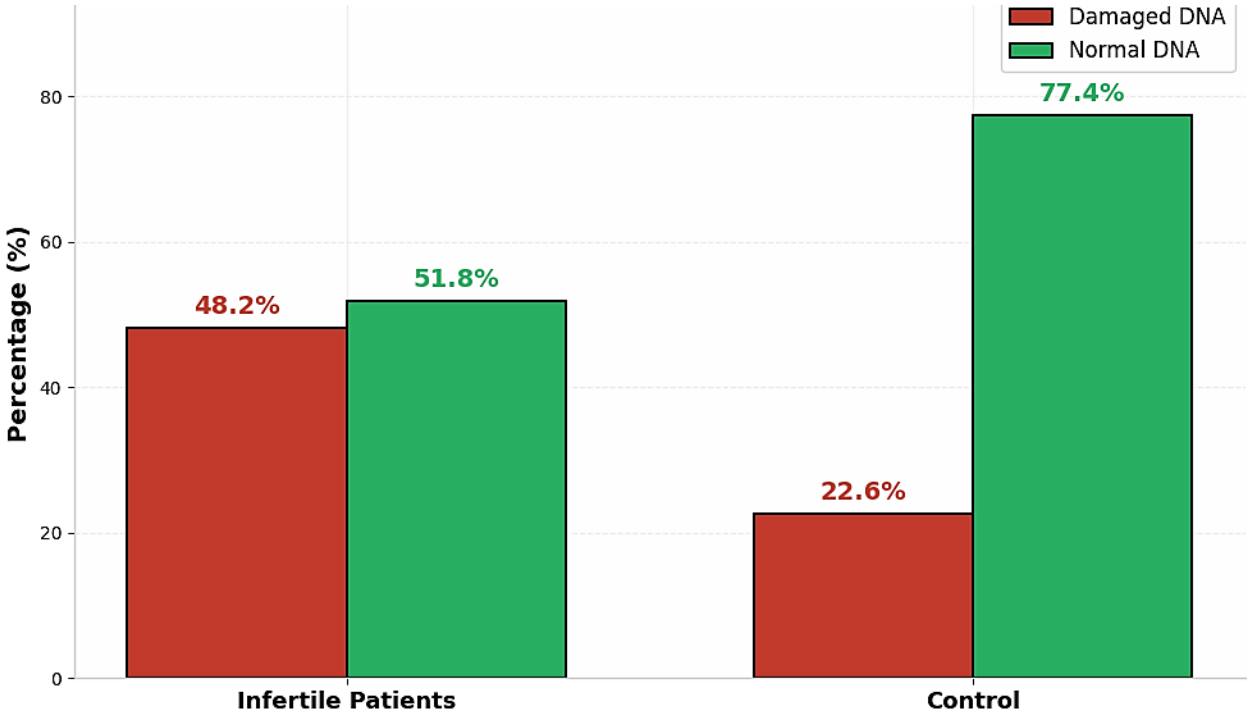

Figure 2. Percentage of sperm DNA fragmentation between infertile and healthy men

As seen in Table 3, all of the previous studies illustrated similar values of stress hormone levels between the infertile groups allocating to poor, and balance sperm DNA integrity. The mean serum levels of cortisol and ACTH were both significantly higher in men with DNA damage compared to those without, (P = 0.006 and P = 0.007 respectively). Conclusions: These results indicate that exaggerated activation of the hypothalamic–pituitary–adrenal (HPA) axis might be linked to sperm chromatin abnormalities and DNA damage. In comparison, in the damaged DNA group mean DHEA level was also lower but this difference did not reach statistical significance (P = 0.130).

Table 3. Comparison of levels of hormones between infertile men with normal and those with damaged DNA

Hormones	Damaged DNA (N= 29)		Normal DNA (N= 31)		(P value)
	Mean	SD	Mean	SD	
Cortisol (µg/dL)	23.41	4.83	18.47	3.95	0.006 *
ACTH (pg/mL)	46.28	7.91	39.15	6.84	0.007 *
DHEA (µg/dL)	170.53	36.42	186.74	40.18	0.13

*** High Significant at P value <0.01**

Discussion

This study aims to determine if there is an association between stress-related hormones and sperm DNA fragmentation in men diagnosed with unexplained infertility. Results: Infertile men had a significantly higher serum cortisol and ACTH levels than healthy fertile controls (P < 0.05) while showing a significant reduction in DHEA compared with the compared

group ($P < 0.001$). More importantly, cortisol and ACTH levels were significantly higher in infertile men with disrupted sperm DNA than in those without alteration of DNA integrity; whereas the DHEA values were similar between both subgroups. These results indicate a possible role of HPA axis activation in sperm DNA damage and male reproductive dysfunction. No significant differences in age, BMI and residence were observed between the infertile patients and healthy controls (Table 1). Such comparability reduces the impact of potential confounders and reinforces the reliability of observed relationships between hormonal changes and disease status with regards to infertility. Similar matching strategies were recommended in reproductive studies to isolate endocrine differences due to infertility as opposed to demographic differences (Agarwal et al., 2017).

The most important discovery in this study was that there was a significant increase in serum cortisol level among infertile men. Cortisol is the most important glucocorticoid hormone that responds to physiologic and psychological stressors associated with specific markers of HPA-axis activation. Some studies have reported that chronic elevation of cortisol has negative effects on male reproductive function, as the secretions of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH) and testosterone are all inhibited due to increased secretion of cortisol (Whirledge & Cidlowski, 2010). In addition, too much cortisol could also heighten oxidative stress in the testes and subsequently reduce spermatogenesis and sperm function. Our current findings are in line with those reported by Nordkap et al (2016), which noticed that psychological stress and increased stress biomarkers were contained to inferior semen quality status and reproductive potential. Similarly, Janevic et al. (2014) revealed that men under increased stress have been shown to exhibit decreased sperm quantity and motility suggesting that hormonal components of the stress response are injurious to male reproduction.

The levels of ACTH were also significantly elevated in infertile men compared to controls. To that end, ACTH induces the secretion of cortisol from the adrenal cortex and thus serves as a measure of activation of a stress response system. The finding of significantly increased ACTH levels in the current report provides additional evidence for a state of chronic neuroendocrine stress in men with infertility (Klimek et al., 2005). Previous studies have shown that chronic stimulation of the HPA axis, for example by exogenous glucocorticoids when administered at supraphysiological doses or by stress itself, can suppress reproductive hormone secretion and ultimately reduce spermatogenic activity. Thus, the rise in ACTH seen in infertile men may represent a key mechanism linking psychological and physiological stress to reproductive dysregulation (Rivier & Rivest, 1991).

In contrast, DHEA was statistically significantly lower in infertile men than healthy controls. DHEA: Dehydroepiandrosterone (DHEA) is an adrenal steroid acting principally as a precursor for androgen synthesis and has antioxidant and anti-glucocorticoid properties. Inhibition of the negative effect of cortisol on oxidative homeostasis may become more competent by decreasing levels of DHEA, progressively enhancing the oxidative damage in effectivity on the reproductive milieu (Lin et ail., 2025). These observations are consistent with reports from Labrie et al. (2005) proposed that DHEA plays a role in retaining endocrine balance and reproductive status via its androgenic and protective actions. Thus, decreased availability of DHEA can affect spermatogenesis and poor fertilization results.

One of the other significant findings observed was between stress hormones and sperm DNA. Our major findings were that levels of cortisol and ACTH in the first of two blood samples taken from men with damaged sperm DNA were significantly higher than those in men with normal DNA integrity. Over the past decade, sperm DNA fragmentation has become recognized as one of the most important markers of male fertility as it directly affects fertilization, embryo development and implantation, with implications for pregnancy outcomes (Sakkas & Alvarez, 2010). Increased cortisol may play a role in the fragmentation of DNA through dual mechanisms by induction of oxidative stress and increased production of reactive oxygen species (ROS). High levels of ROS may compromise antioxidant defenses, are associated with chromatin instability and DNA strand breaks; all leading to sperm dysfunction (Agarwal et al., 2014).

This finding in the current study is well-supported by the previous literature that found that higher stress hormones associated with sperm DNA damage. Oxidative stress is one of the important pathways causing sperm DNA fragmentation in infertile men (Panner Selvam and Agarwal 2018). In line with this, Aitken and Baker (2020) highlighted how exposure to environmental and physiological stressors exacerbate oxidative damage to sperm chromatin that ultimately compromises male fertility. The markedly elevated cortisol and ACTH in men with DNA damage observed in the present study supports that stress-mediated oxidative mechanisms can result in sperm DNA damage.

Notably, despite lower DHEA levels in the damaged DNA group, this difference did not achieve statistical significance. The finding indicates that both cortisol and ACTH are more closely associated with sperm DNA integrity than DHEA (Zini et al., 2001). DHEA may impact fertility mainly through endocrine and metabolic

pathways rather than directly affecting chromatin stability. On the other hand, the lack of significance could be due to the relatively small number of samples for a subgroup analysis. Larger studies with regimens are needed to better elucidate its role in sperm DNA protection (Xu et al., 2019).

Conclusion

This study indicated that serum stress-related hormones alterations pre- and post-coital or during ovulatory cycle were associated with increased sperm DNA damage and can represent a male factor involved in unexplained male infertility. The increased concentrations of cortisol and ACTH likely influence the regulation of sperm quality through mechanisms that affect testicular function in response to stress. A reduction in DHEA could compromise even more the body's ability to prevent hormonal and oxidative imbalance, In summary, the results underscore the possible application of stress management and endocrinological assessment in the evaluation and management of men with idiopathic infertility.

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