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Research Article

Patterns Some Oxidative Stress Markers (MDA, GSH), C-Reactive Protein and Reproductive Hormones in Infertile Male Subjects in Owerri

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Abstract

Oxidative stress, inflammation, and hormonal imbalance have been implicated in the pathophysiology of male infertility. This study evaluated the serum levels of oxidative stress markers (MDA and GSH), C-reactive protein (CRP), and reproductive hormones (FSH, LH, and testosterone) in infertile male subjects in Owerri. A cross-sectional, case-control study was conducted at Imo State Specialist Hospital, Umuguma, involving 144 participants, including 72 infertile and 72 healthy control subjects, aged 25–50 years. Serum MDA and GSH concentrations were determined using spectrophotometric methods, while CRP, FSH, LH, and testosterone levels were measured using enzyme-linked immunosorbent assay (ELISA) techniques. The data generated were subjected to Statistical Analysis using SPSS version 23. Tests with a probability value of $p<0.05$ were considered statistically significant, and the results were expressed as mean ± SD. The results showed that male infertile subjects demonstrated significantly higher serum MDA (3.33 ± 0.62 µmol/L) and CRP (2.78 ± 0.93 mg/L) levels, alongside lower GSH (1.71 ± 0.34 µmol/L) and Testosterone (7.32 ± 4.99 nmol/L) concentrations compared to fertile controls (MDA 1.85 ± 0.49 µmol/L), (CRP 0.89 ± 0.24 mg/L), (GSH 3.77 ± 0.78 µmol/L), (Testosterone 16.04 ± 4.86 nmol/L) ($p < 0.05$ in each case). Additionally, there were significantly lower levels of FSH (10.82 ± 3.91 IU/L) and LH (6.94 ± 2.60 IU/L) compared to controls (FSH 16.39 ± 3.03 IU/L, LH 9.40 ± 2.72 IU/L), suggesting disruptions in the hypothalamic-pituitary-gonadal axis In conclusion, higher serum levels of MDA and CRP, with concomitant lower levels of GSH, FSH, LH, and testosterone, were observed in male infertile subjects, implicating oxidative stress, systemic inflammation, and hormonal imbalance in male infertility.

Keywords: oxidative stress markers; MDA; GSH; C-reactive protein; reproductive hormones; infertile male; Owerri

Introduction

Millions of couples worldwide are impacted by infertility, which is still a major public health concern. A number of interconnected factors, including genetic defects that impair normal reproductive activities, contribute to the complexity of this disorder [1]. Along with lifestyle decisions like food, exercise, and substance use that negatively impact fertility, these hormone imbalances also hinder sperm production and quality. Additionally, it is becoming more widely acknowledged that exposure to industrial chemicals and other pollutants in the environment has a significant role in the aetiology of male infertility. A thorough grasp of the complex interactions between these elements is essential for developing practical solutions to couples' infertility problems [2].

Despite not being a life-threatening condition, infertility frequently causes significant psychological, physical, and emotional misery in addition to social and socioeconomic consequences. Because infertility-related problems can lead to stigmatisation, disinheritance, isolation, and even divorce, infertility has enormous societal ramifications in Nigeria . Because infertility has always been viewed primarily as a female problem, harmful sociocultural narratives that place all the blame for infertility on women are perpetuated. A number of physiological functions, such as normal sperm generation, concentration, transport, and release, as well as functional motility, are required for this complex state. The chance of a successful fertilisation and subsequent pregnancy can be significantly reduced by any interference with these processes [3]

This worsened state of affairs, which reflects complex social, medical, and environmental factors that affect reproductive health, has important ramifications for family planning, personal health, and more general public health issues. Male infertility is a complex aetiology that includes immune system dysfunction, genetic abnormalities, sperm-related abnormalities, hormonal imbalances, environmental exposures, and lifestyle variables like alcohol, tobacco, and obesity. Male infertility can still have an idiopathic origin in some situations. There is mounting evidence that the pathophysiology of male infertility is significantly influenced by oxidative stress. Oxidative stress can result from a number of factors that upset the equilibrium between oxidants and antioxidants, such as environmental stressors, excessive physical activity, and antioxidant deficits [4].

An imbalance between the generation of reactive oxygen species (ROS) and the body's capacity to use antioxidants to mitigate their harmful effects is known as oxidative stress. This imbalance may occur as a result of either a depletion of antioxidant defences, which are vital for shielding the body from oxidative damage, or an excess of ROS, an unstable chemical that can harm cellular components [5].

Reactive oxygen species (ROS) are extremely reactive oxygen-containing molecules that are essential to many biological functions. These chemicals are mostly produced as metabolic byproducts of several enzymatic processes and mitochondrial respiration. ROS have a dual character in the context of male reproduction, impacting reproductive health in both positive and negative ways . When ROS are present in balanced and controlled amounts, they have a positive impact on vital physiological processes like intercellular signalling that controls sperm function and fertility and sperm capacitation, which gives sperm the ability to fertilise an egg. The acrosome reaction is also essential for allowing sperm to pass through the protective layers of the egg [6]

On the other hand, extremely high ROS levels can cause a pathological state and set off a series of cellular damaging events that impair sperm function. The delicate balance necessary for the best reproductive health is highlighted by the fact that this oxidative stress can reduce fertility by compromising sperm quality and impairing motility [7]. The degree of oxidative stress and its effect on male fertility can be evaluated using a number of indicators.

Lipid peroxidation, a process in which free radicals target lipids in cell membranes and cause cellular damage, produces malondialdehyde (MDA) as a byproduct [8] Elevated levels of MDA, a crucial indicator of oxidative stress, indicate an imbalance between the body's capacity to counteract the negative effects of reactive oxygen species (ROS) and their generation (Aitken et al, 2022). Because high MDA concentrations might damage sperm membrane integrity, affecting their function and motility, they are especially worrying when it comes to male fertility [9].

It has been shown that males who are infertile frequently have far higher MDA levels than guys who are naturally fertile. This rise in MDA is a sign of increased lipid peroxidation, which can lower overall reproductive potential in addition to endangering sperm viability [10]). The correlation shown between elevated MDA levels and male infertility highlights the significance of oxidative stress as a contributing element to issues related to reproductive health.

Every cell in the human body contains glutathione (GSH), a vital tripeptide molecule made up of the amino acids cysteine, glutamine, and glycine. Reactive oxygen species (ROS) are unstable chemicals that can harm cells when they are produced in excess. This potent antioxidant is essential in defending cells against oxidative damage caused by ROS [11]. By neutralising this ROS, GSH lessens the damaging effects of these substances. It also supports the activity of glutathione peroxidase, a crucial enzyme that aids in the detoxification of toxic metabolic byproducts. Oxidative stress and GSH levels have a substantial link; in particular, oxidative stress and GSH levels are inversely correlated. Accordingly, oxidative stress is often lower when GSH levels are high, but lowered GSH levels are suggestive of higher levels of oxidative stress in the body [12]

Studies have shown that males who are infertile frequently have lower GSH levels. In the end, this depletion may reduce fertility by adversely affecting sperm motility and viability, among other aspects of sperm function . Since antioxidant defences are essential for optimum cellular function and general well-being, the relationship between glutathione and reproductive health emphasises how important it is to maintain sufficient levels of them.

One important indicator for the body's chronic inflammation is C-reactive protein (CRP). The liver produces this protein in reaction to inflammation, and a number of underlying medical conditions, including as oxidative stress, autoimmune diseases, and infections, can cause its levels to rise noticeably [13]. A troubling association between high CRP levels and male infertility has been brought to light by recent research. Reproductive health may suffer from chronic inflammation, which is indicated by a sustained rise in CRP. In particular, inflammation can directly harm sperm by altering their shape and function, which lowers their potential for overall fertility [14]. This connection implies that controlling long-term inflammation could be crucial to treating male infertility. Because CRP is a marker, tracking its levels may provide important information about a person's general health and fertility problems. Men who suffer from inflammation may have better reproductive outcomes if they take proactive measures to lower it, such as changing to a healthier lifestyle [15].

The anterior pituitary gland secretes a critical hormone called follicle-stimulating hormone (FSH), which is essential for both male and female reproduction. Sperm production in men is regulated by FSH, which stimulates the Sertoli cells in the testes to assist spermatogenesis, the process by which sperm cells are generated and mature. Elevated FSH levels may indicate poor spermatogenesis, a condition in which there are underlying problems with sperm generation. Hormonal imbalances, genetic diseases, or testicular injury are some of the causes of this syndrome. Oxidative stress, which happens when the body produces too many reactive oxygen species, is a major factor in poor spermatogenesis [16]

Another important hormone that is produced and secreted by the anterior pituitary gland that is essential to the endocrine system is luteinizing hormone (LH). Male reproductive health depends on the synthesis of testosterone, which is regulated by this hormone . The development of male secondary sexual characteristics and sperm maturation are supported when LH levels are within the normal range because they encourage the production of testosterone by the Leydig cells in the testes. However, this delicate hormonal balance can be seriously upset by anomalies in LH levels, whether they are abnormally high or low. Sperm development and overall fertility may be directly impacted by low LH levels, which can result in insufficient testosterone production. On the other hand, abnormally elevated LH levels may be a sign of an issue with the hormone regulatory feedback loop, which is frequently linked to diseases like primary hypogonadism or testicular failure. Abnormal LH levels can have serious repercussions, impacting not only fertility but also the body's hormonal balance and general reproductive health [17]

The testes are the primary source of testosterone, a powerful steroid hormone that is essential to sperm formation and maturation. This hormone affects everything from desire to the general health of sperm cells, and it is crucial

for the regulation of several processes associated with male reproductive health. Sperm production might be seriously hampered by a decline in testosterone levels. Decreased testosterone frequently leads to lower fertility by adversely affecting the number and quality of sperm. Moreover, sperm function and viability may be further jeopardised by reduced testosterone's correlation with elevated oxidative stress in the reproductive system . The significance of preserving ideal testosterone levels for reproductive health and successful conception is shown by this association [18].

This study will aim to shed light on the underlying causes of male infertility and find possible biomarkers for diagnosis and treatment by investigating the association between these biomarkers (MDA, GSH, CRP, FSH, LH, and testosterone) and oxidative stress in infertile men.

Research on the hormonal and biochemical profiles linked to male infertility in Nigeria, namely in the Owerri region, is severely lacking. Prior studies have brought attention to this deficiency, including those carried out by Edward et al. in 2023. Given the startlingly high rates of male infertility in the nation, this study aims to close this important knowledge gap and offer insightful information about the underlying causes of this problem.

Determining the underlying processes of male infertility requires an understanding of the biochemical and hormonal profiles of those who have this illness. According to Kaya et al. (2024), insights obtained from these profiles can provide insight into the intricate pathophysiology linked to male infertility. Acquiring this knowledge not only improves our comprehension of the illness but also greatly influences the creation of more focused and efficient diagnostic techniques as well as treatment plans that are adapted to the unique requirements of those who are impacted. The study's conclusions have the potential to significantly influence healthcare policy with relation to the identification and management of male infertility (Oluwole et al., 2021). This research can help policymakers create focused and efficient solutions by clarifying the particular biochemical and hormonal characteristics associated with male infertility. These tactics may result in better health results for people who are impacted, which would raise the standard of care and assistance offered to those who are struggling with infertility. This customised strategy guarantees the effective use of healthcare resources while attending to the particular requirements of this patient group [19].

Male infertility affects millions of couples worldwide and is a serious public health concern. The prevalence of male infertility is especially alarming in Nigeria, where estimates indicate that over 32% of males struggle with infertility. In order to improve the reproductive health and well-being of couples who are impacted by male infertility, this study intends to provide light on this urgent topic and may be crucial in guiding the development of efficient solutions.

Materials and Methods

Study Area

The study was conducted at Imo State Specialist Hospital, Umuguma, Owerri West LGA. Owerri, the vibrant capital city of Imo State, is nestled in the enchanting south-eastern region of Nigeria, West Africa. Geographically positioned between latitudes 5°25' and 5°35'N and longitudes 6°55' and 7°05'E, this city boasts a unique location that contributes to its diverse culture and rich heritage. According to the 2024 population estimate, the population of Owerri West LGA was recorded at approximately 401,000 people. (World Population Review)

Advocacy, Mobilization, and Pre-Survey Contact

The ethical approval was obtained from Imo State Specialist Hospital, Umuguma, Owerri

Study Population and Sample Size

A total of 144 participants were studied at the Imo State Specialist Hospital, Umuguma, Owerri. These participants involved 72 male infertile patients who came to seek treatment at the obstetric and gynaecology clinic located at Imo State Specialist Hospital Umuguma, Owerri, and 72 healthy fertile male control subjects. The selection of patients was conducted through a thorough assessment process that included evaluating their medical history, a comprehensive physical examination, and relevant laboratory test results to ensure eligibility and suitability for the study.

Criteria for selection

(i) Inclusion Criteria

Participants in this study met the following criteria:

i. Participants were male individuals between the ages of 25 - 50 years old.

ii. Married men in active intercourse for at least one year without fathering a child

iii. Candidates had undergone semen analysis to confirm the diagnosis of infertility.

iv. Eligible participants were actively attending the infertility clinic located at Imo State Specialist Hospital Umuguma, Owerri

v. All individuals that took part in the study consented to it, indicating their understanding of the study's purpose and procedures, as well as their voluntary decision to participate.

(ii) Exclusion Criteria

Participants were excluded from the study under the following circumstances:

i. Subjects who were on medication that might negatively impact fertility or who had recently taken antioxidants or supplements that might affect oxidative stress markers and those on hormonal and corticosteroids.

ii. Participants who declined to provide informed consent.

iii. Individuals with a previous diagnosis of orchitis, epididymitis, or testicular torsion were not eligible. These conditions could lead to complications that might influence fertility outcomes.

iv. Those who had undergone a vasectomy or any other surgical intervention that could potentially impact their fertility were excluded from participation. Such procedures might irreversibly alter reproductive capabilities.

v. Patients diagnosed with known medical conditions that could adversely affect fertility, such as diabetes mellitus or hypertension, were excluded. These health issues could lead to hormonal imbalances or vascular problems that might compromise reproductive health.

vi. Finally, individuals currently taking medications that are known to interfere with fertility, including but not limited to steroids or chemotherapy agents, were not eligible for the study. The effects of these drugs could significantly alter hormonal levels or sperm production, affecting study outcomes.

Study Design

The research design was a cross-sectional study focused on male infertility. The study involved two groups: male subjects diagnosed with infertility and a control group of fertile men. The investigation proceeded through the following stages:

Sample Collection

Five millilitres of blood were collected aseptically from the antecubital vein by venepuncture from each subject. The blood samples were then dispensed into plain tubes and immediately labelled for proper identification, after which, allowed to clot. The serum was separated using a Pasteur pipette, transferred into sterile sample tubes, and stored at -20ºC before testing.

Laboratory Procedures

All reagents were commercially procured, and the manufacturer's standard operating procedures were strictly followed.

- **Determination of Serum Malondialdehyde by Thiobarbituric acid-reactive substance (TBARS) assay**
- **Determination of Serum Glutathione (GSH) by Spectrophotometric Assay**
- **Determination of Serum C-reactive protein (CRP) by enzyme-linked immunosorbent assay**
- **Determination of Serum FSH by enzyme-linked immunosorbent assay**
- **Determination of Serum LH by enzyme-linked immunosorbent assay**
- **Determination of Serum Testosterone by competitive enzyme-linked immunosorbent assay**

Statistical Analysis

The data collected from this study were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23. Descriptive statistics, including means, standard deviations, were used to calculate the distributions of the outcome variables (FSH, LH, testosterone, CRP, and oxidative stress biomarkers).

Inferential statistics were used to test the hypotheses and answer the research questions. Specifically, a t-test was used to compare the means of FSH, LH, testosterone, and oxidative stress biomarkers between the two groups (e.g., fertile vs. infertile men), A p-value of less than 0.05 was considered statistically significant for all analyses.

Results

Table 1: Mean ± SD values of MDA, GSH, CRP, FSH, LH, and Testosterone in infertile male and control subjects, n=72

Variables (Units)	Infertile Male Subjects n = 72	Male control subjects n =72	t-value	p-value
MDA (µmol/L)	3.33 ± 0.62	1.85 ± 0.49	15.110	0.001
Lower 95% C.I	3.18	1.73		
Upper 95% C.I	3.48	1.96		
GSH (µmol/L)	1.71 ± 0.34	3.77 ± 0.78	-20.470	0.001
Lower 95% C.I	1.63	3.59		
Upper 95% C.I	1.79	3.96		
CRP (mg/L)	2.78 ± 0.93	0.89 ± 0.24	16.520	0.001
Lower 95% C.I	2.56	0.83		
Upper 95% C.I	2.99	0.94		
FSH (IU/L)	10.82 ± 3.91	16.39 ± 3.03	-10.990	0.001
Lower 95% C.I	9.90	15.67		
Upper 95% C.I	11.75	17.10		
LH (IU/L)	6.94 ± 2.60	9.40 ± 2.72	-9.480	0.001
Lower 95% C.I	6.33	8.76		
Upper 95% C.I	7.55	10.04		
Testosterone (nmol/L)	7.32 ± 4.99	16.04 ± 4.86	-11.320	0.001
Lower 95% C.I	6.15	14.89		
Upper 95% C.I	8.49	17.18		

Value is statistically significant at P<0.05

The analysis from the table 1 compared the oxidative stress markers (MDA, GSH), CRP and reproductive hormones between male infertile subjects and

healthy controls. All variables showed statistically significant differences (p=0.000). There were significantly higher levels of **MDA** (3.33 ± 0.62 **µmol/L) and CRP (2.78** ± 0.98 **mg/L) in male infertile subjects, compared to control respectively (1.85** ± 0.49 **µmol/L, 0.89** ± 0.24 mg/L) (p=0.001 in each case). **GSH** (1.71 ± 0.34 **µmol/L), FSH (10.82** ± 3.91 IU/L), **LH** (6.94 ± 2.60 IU/L), and Testosterone (7.32 ± 4.9 **nmol/L) were significantly lower in male infertile subjects compared to controls, respectively (3.77** ± 0.78 **µmol/L, 16.39** ± 3.03 IU/L, 9.40 ± 2.72 IU/L and 16.04 ± 4.86 nmol/L) (p=0.001 in each case)

Discussion

MDA, a known indicator of oxidative stress and lipid peroxidation, was considerably greater in the infertile group (3.33 ± 0.62 µmol/L) than in the controls (1.85 ± 0.49 µmol/L) (p = 0.001). Increased oxidative damage to testicular tissues and spermatozoa was indicated by elevated MDA levels. It is well recognised that reactive oxygen species (ROS) lower reproductive potential by affecting sperm motility, morphology, and DNA integrity [20]. This demonstrated that one of the main causes of male infertility is oxidative stress.

Male infertiles' GSH levels were substantially lower (1.71 ± 0.34 µmol/L) than those of fertile controls (3.77 ± 0.78 µmol/L), with p = 0.001. One important intracellular antioxidant that protects against ROS is GSH. A reduction in GSH may weaken the antioxidant defence mechanism and encourage oxidative damage in sperm. A redox imbalance that promoted oxidative stress and interfered with spermatogenesis was the cause of the substantial drop in GSH among infertile men.

Infertile patients had significantly higher levels of CRP, a measure of systemic inflammation, (2.78 ± 0.93 mg/L) than controls (0.89 ± 0.24 mg/L) (p = 0.001). Testicular dysfunction and decreased spermatogenesis have been linked to chronic low-grade inflammation [21]. The elevated CRP levels indicated that oxidative stress and hormonal imbalance in infertile men may be made worse by inflammatory processes.

Compared to controls (16.39 ± 3.03 IU/L), infertile males had considerably lower FSH levels (10.82 ± 3.91 IU/L) (p = 0.001). FSH stimulates Sertoli cells, which is necessary for spermatogenesis. Reduced FSH may be a sign of inflammation or oxidative stress-induced suppression of negative feedback or hypothalamic-pituitary dysfunction [22]. However, recent research revealed that feedback from poor spermatogenesis may cause higher FSH in non-obstructive azoospermia, highlighting the variety of causes of infertility.

Additionally, infertile men had considerably lower levels of LH (6.94 ± 2.60 IU/L) than controls (9.40 ± 2.72 IU/L) (p = 0.001), which controls the generation of testosterone by Leydig cells. Reduced libido, erectile dysfunction, and suboptimal sperm maturation could result from inadequate LH secretion, which could also affect testosterone production [23]. This lends credence to the idea that male infertility is characterised by disruption of the hormonal axis.

Infertile patients had significantly lower testosterone levels (7.32 ± 4.99 nmol/L) than fertile controls (16.04 ± 4.86 nmol/L) (p = 0.001). Spermatogenesis, secondary sexual traits, and libido are all dependent on testosterone. Men who are infertile frequently exhibit hypogonadism, which is frequently brought on by oxidative stress, testicular injury, or hormonal dysregulation [24]. Endocrine insufficiency in the infertile population was underlined by the dramatic drop in testosterone, which mirrored the findings of decreased LH[25].

Conclusion

This study showed that increased MDA and CRP levels, respectively, are indicative of oxidative stress and inflammation. Conversely, elevated levels of reproductive hormones (FSH, LH, and testosterone) and antioxidants (GSH) were reduced.

These findings provide credence to the idea that hormonal profiles and oxidative and inflammatory indicators are important factors that influence male fertility.

The study highlights South-Eastern Nigeria's distinct population background. The results indicate that antioxidant and hormone-based treatment interventions may improve reproductive outcomes and emphasise the necessity of early diagnostic screening utilising these biomarkers.

Indeed, male infertile participants had higher blood levels of MDA and CRP and lower levels of GSH, FSH, LH, and testosterone. This suggests that oxidative stress, systemic inflammation, and hormonal imbalance are factors in male infertility.

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