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## Association of Oxidative Stress and Energy Metabolism with Sperm Quality in Chinese Men: A Postprint

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### Abstract

**Background** Oxidative stress and energy metabolism are important factors affecting sperm quality in male individuals. However, existing studies are mostly animal experiments, lacking population evidence, and previous research has focused more on exploring the effects of oxidative stress and energy metabolism on sperm density and motility, with a lack of studies on sperm movement speed and trajectory.

**Objective** To investigate the relationship between oxidative stress and energy metabolism-related biological indicators and various parameters of male sperm including density, motility, movement speed, and movement trajectory, and to provide epidemiological evidence for precise intervention of male reproductive health.

**Methods** From June to December 2021, 109 volunteers were recruited at the Reproductive Medicine Center of Xijing Hospital, their semen samples were collected, and a Computer-Aided Sperm Analysis system (CASA) was used to detect more than 10 parameters including sperm density, motility, movement speed, and movement trajectory. The levels of malondialdehyde (MDA) and reduced glutathione (GSH) in semen samples were measured to reflect oxidative stress levels, and the level of adenosine triphosphate (ATP) was measured to assess energy metabolism levels. Generalized Linear Models (GLM) were applied to evaluate the associations between oxidative stress indicators (MDA, GSH) and energy metabolism indicators (ATP) with various sperm quality parameters.

**Results** A total of 67 sperm samples were used to detect oxidative stress levels, and 42 sperm samples were used to assess energy metabolism levels. GLM analysis showed that MDA, GSH, and ATP levels were all associated with

multiple parameters including sperm motility, movement speed, and movement trajectory, but showed no significant association with sperm density.

**Conclusion** Higher oxidative stress levels and lower energy metabolism levels are associated with decreased sperm motility, reduced movement speed, and adverse changes in sperm trajectory in men. This study provides a basis for using supplements that reduce oxidative stress and improve energy metabolism to enhance male sperm quality.

## Full Text

### Association Between Oxidative Stress, Energy Metabolism, and Sperm Quality in Chinese Men

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## Abstract

**Background:** Oxidative stress and energy metabolism are critical factors affecting sperm quality in male individuals. However, most existing studies are animal experiments lacking human population evidence, and previous research has primarily focused on the effects of oxidative stress and energy metabolism on sperm concentration and motility, with limited investigation into sperm movement velocity and trajectory.

**Objective:** To investigate the relationships between oxidative stress and energy metabolism-related biological indicators and various sperm parameters including density, motility, movement velocity, and trajectory, thereby providing epidemiological evidence for precise intervention of male reproductive health.

**Methods:** From June to December 2021, 109 volunteers were recruited at the Reproductive Medicine Center of Xijing Hospital. Semen samples were collected and analyzed using a Computer-Aided Sperm Analysis (CASA) system to detect more than 10 parameters including sperm density, motility, movement velocity, and trajectory. Malondialdehyde (MDA) and reduced glutathione (GSH) levels in semen samples were measured to reflect oxidative stress status, while adenosine triphosphate (ATP) levels were assessed to evaluate energy metabolism status. Generalized linear models (GLM) were applied to evaluate the associations between oxidative stress indicators (MDA, GSH) and energy metabolism indicators (ATP) with various sperm quality parameters.

**Results:** A total of 67 sperm samples were used to detect oxidative stress levels, and 42 sperm samples were used to assess energy metabolism levels. GLM analysis showed that MDA, GSH, and ATP levels were all associated with multiple parameters of sperm motility, movement velocity, and trajectory, but showed no significant association with sperm density.

**Conclusion:** Higher oxidative stress levels and lower energy metabolism levels are associated with reduced sperm motility, decreased movement velocity, and adverse changes in sperm trajectory. This study provides evidence for improving male sperm quality through supplements that reduce oxidative stress and enhance energy metabolism.

**Keywords:** Sperm quality; Oxidative stress; Energy metabolism; Male reproductive health

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## Introduction

Declining sperm quality has become a serious global problem affecting male reproductive health [1-5]. According to a recent meta-analysis, over the past 40 years, the average sperm count and concentration in adult men worldwide have decreased by 60% and 52%, respectively, and this declining trend continues [2]. In addition to the rapid decline in sperm number and concentration, the sharp decrease in sperm motility has exacerbated male reproductive health issues [6]. For example, a cohort study collecting 9,425 semen samples from 489 adult men found significant declines in total sperm motility and progressive motility [6]. Given the increasingly serious problem of male reproductive health, investigating its risk factors and biological mechanisms is of great significance [1].

Although the specific biological mechanisms underlying declining sperm quality have not been fully elucidated [7], oxidative stress and energy metabolism may be the primary mechanisms [8-10]. Studies have shown that elevated oxidative stress and reduced energy metabolism are significantly associated with decreased sperm quality [11-13]. For instance, a case-control study recruiting 79 men with teratozoospermia and 56 healthy controls found that oxidative stress levels in

seminal plasma were significantly higher in patients with teratozoospermia than in healthy men [12]. Sperm damage caused by oxidative stress is the main cause of infertility in 30%-80% of men [14]. Meanwhile, energy metabolism plays a key role in spermatogenesis and sperm motility [15]. For example, a vitamin D intervention study showed that higher ATP levels were significantly associated with increased sperm progressive motility [16], possibly by improving the functional status of the mitochondrial oxidative respiratory chain. However, these studies are primarily based on animal experiments, lacking epidemiological evidence from human populations, and it remains unclear which specific sperm quality parameters are mainly affected by oxidative stress and energy metabolism.

Therefore, we conducted a cross-sectional study to systematically evaluate the effects of oxidative stress and energy metabolism levels on various sperm quality parameters and identify which sperm parameters are primarily altered by oxidative stress and energy metabolism levels.

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## Methods

**1.1 Study Subjects and Semen Sample Collection** Volunteers were recruited from patients undergoing semen quality examination at the Reproductive Medicine Center of Xijing Hospital between June and December 2021. Each volunteer completed a brief questionnaire including information on date of birth, education level, height, weight, smoking status (defined as smoking  $\geq 1$  cigarette per day for  $\geq 6$  months continuously or cumulatively), and alcohol consumption (defined as drinking  $\geq 1$  time per week on average) [17]. After 3-7 days of abstinence, semen samples were collected by masturbation into sterile wide-mouth collection bottles. Samples were stored in a 37°C incubator and immediately analyzed for sperm quality and oxidative stress/energy metabolism markers after complete liquefaction.

Inclusion criteria were volunteers recruited from June to December 2021. Exclusion criteria included cryptorchidism, varicocele, untreated reproductive system infections, or previous diagnosis of azoospermia. A total of 109 adult men completed the study.

This study was approved by the Medical Ethics Committee of Xijing Hospital (Code: KY20223104-TEMP), and informed consent was obtained from all participants before the study.

**1.2 Sperm Quality Analysis** Sperm quality analysis was performed according to the 5th edition of the *WHO Laboratory Manual for the Examination and Processing of Human Semen*. Collected semen specimens were first examined by professional technicians for semen volume, color, viscosity, and liquefaction status, which were recorded in an electronic system. After complete liquefaction, 3  $\mu$ l of each subject's semen specimen was placed on a disposable sperm detection plate (Saishi Medical Technology, Beijing, China) and analyzed using

a Computer-Aided Sperm Analysis (CASA) system (Saishi Medical, SAS) with SASII® version 2.3 software to evaluate specific parameters including sperm density, motility, movement velocity, and trajectory such as curvilinear velocity, amplitude of lateral head displacement, and beat frequency. A schematic diagram of the CASA system detecting multiple sperm movement parameters is shown in [Figure 1: see original paper].

To ensure reliability of sperm quality test results, all analyses in this study were performed on the same sperm quality analyzer. The analyzer had passed the inter-laboratory quality control assessment of the Northwest Reproductive Medicine Alliance and was certified as qualified and in control. During the study period, all sperm quality tests were completed by the same technician to avoid personnel error. Additionally, the sperm quality analyzer was calibrated monthly using standard concentration glass powder for concentration assessment, video-based quality control for sperm motility analysis, and error analysis by comparing CASA system results with manual methods. The analyzer met all error requirements during the study period.

**1.3 Assessment of Oxidative Stress and Energy Metabolism** This study assessed oxidative stress levels by measuring malondialdehyde (MDA) and reduced glutathione (GSH) in seminal plasma specimens. MDA is one of the most common products of polyunsaturated fatty acid peroxidation and has been widely used to evaluate oxidative stress levels [18], serving as a direct indicator of lipid peroxidation in seminal plasma [19]. Higher MDA levels represent higher oxidative stress levels. GSH is part of the non-enzymatic antioxidant defense system that protects lipids, proteins, and nucleic acids from oxidative damage, with higher GSH levels indicating higher antioxidant capacity and lower oxidative stress levels.

MDA assay kit (#BC0025, Solarbio, Beijing) and GSH assay kit (#BC1175, Solarbio, Beijing) were used to detect oxidative stress levels in collected semen specimens. After sperm quality analysis, remaining semen samples were centrifuged at 800g for 15 minutes at room temperature, and 2ml of the supernatant was transferred to EP tubes. The samples were then centrifuged at 10,000g for 30 minutes, and the supernatant was collected. Seminal plasma samples were divided into several equal portions, and MDA and GSH levels were strictly measured according to the kit protocols.

Energy metabolism level was assessed by detecting ATP in semen specimens. Higher ATP levels indicate better energy supply for sperm motility and fertilization. An enhanced ATP assay kit (#S0027, Beyotime, Shanghai) was used for detection. Two milliliters of 50% Percoll solution was added to a 15ml centrifuge tube, the pellet was resuspended in 2ml phosphate buffer solution (PBS), and then centrifuged at 1000g for 20 minutes at room temperature. After removing the supernatant, 2ml PBS was added to wash once, and the final pellet was immediately used to assess semen ATP levels.

Due to the limited volume of semen that could be collected in a single ejaculate and the fact that prolonged storage or freeze-thaw cycles would affect the accuracy of oxidative stress and energy metabolism measurements, collected semen specimens were divided into two portions for separate detection of oxidative stress markers (MDA and GSH) and energy metabolism markers (ATP).

**1.4 Statistical Analysis** All variables were first described statistically. For continuous variables, mean  $\pm$  standard deviation was used if normally distributed, and median (interquartile range) if skewed. Categorical variables were described using frequency (percentage). Generalized linear models (GLM) were then applied to evaluate the relationships between MDA, GSH, and ATP with various sperm quality parameters. Effect estimates were expressed as changes in sperm quality parameters and 95% confidence intervals (95%CI) per 1 nmol/ml increase in MDA, per 10 g/ml increase in GSH, and per 1 nmol/mg protein increase in ATP level.

To adjust for potential confounders and test result robustness, the study included crude and adjusted models. GLM fitting was first performed without any covariates (crude model). Then, semen volume, participant age, body mass index (BMI), education level, smoking status, and alcohol consumption were included as covariates in the model (adjusted model).

Statistical analysis was performed using R software (version 4.1.2), with two-sided  $P < 0.05$  considered statistically significant.

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## Results

**2.1 Descriptive Statistics** This study included 109 adult men. Participants and their semen samples were divided into two groups (oxidative stress group and energy metabolism group). Sixty-seven semen samples were used to examine the relationship between MDA, GSH and sperm quality parameters, and 42 semen samples were used to assess the impact of ATP on sperm quality parameters. The oxidative stress group had a mean age of  $30.04 \pm 4.29$  years, MDA content of  $2.78 (1.69)$  nmol/ml, and GSH content of  $113.54 (74.21)$  g/ml. The energy metabolism group had a mean age of  $32.33 \pm 5.24$  years and ATP content of  $6.61 (2.26)$  nmol/mg protein. Details are shown in .

**TABLE:1** Statistical description of basic demographics, oxidative stress, energy metabolism and sperm quality parameters

**2.2 Relationship Between Oxidative Stress and Sperm Quality Parameters** The relationship between MDA levels and sperm quality parameters is detailed in . After adjusting for age, education level, BMI, smoking, alcohol consumption, and semen volume differences, MDA showed significant associations with multiple parameters. For sperm density, each 1 nmol/ml increase in MDA was associated with a

$5.05 \times 10^6$  ml decrease in progressive sperm density ( $95 \times 10^6$ ,  $-0.06 \times 10^6$ ). For sperm motility, each 1 nmol/ml increase in MDA was associated with a 6.72% decrease in total motility (95%CI: -10.50%, -2.94%), a 5.37% decrease in progressive motility (PR) (95%CI: -8.65%, -2.08%), and a 1.35% decrease in non-progressive motility (NP) (95%CI: -2.36%, -0.35%). For sperm movement velocity, each 1 nmol/ml increase in MDA was associated with a 5.39 m/s decrease in curvilinear velocity (95%CI: -8.31, -2.47), a 2.38 m/s decrease in straight-line velocity (95%CI: -3.83, -0.92), and a 2.98 m/s decrease in average path velocity (95%CI: -4.70, -1.25). Additionally, several sperm trajectory parameters changed significantly: each 1 nmol/ml increase in MDA was associated with a 0.05 m decrease in average lateral head displacement (95%CI: -0.09, 0.00), a 1.49 Hz decrease in average beat frequency (95%CI: -2.35, -0.63), a 1.34° decrease in average movement angle (95%CI: -2.04°, -0.67°), a 1.34% decrease in linearity (95%CI: -2.63%, -0.06%), a 1.07% decrease in oscillation (95%CI: -2.10%, -0.05%), and a 1.55% decrease in forward progression (95%CI: -2.69%, -0.42%).

**TABLE:2** Correlation between MDA in seminal plasma and sperm concentration, motility, movement velocity and trajectory

The study also found that GSH levels were associated with multiple parameters including progressive sperm density, sperm motility, movement velocity, and trajectory. Each 10 g/ml increase in GSH was associated with a  $1.77 \times 10^6$  ml increase in progressive sperm density ( $95 \times 10^6$ ,  $3.28 \times 10^6$ ), a 1.70% increase in total motility (95%CI: 0.51%, 2.90%), and a 1.44% increase in PR (95%CI: 0.42%, 2.47%). For sperm movement velocity, each 10 g/ml increase in GSH was associated with a 0.90 m/s increase in curvilinear velocity (95%CI: -0.07, 1.86), a 0.53 m/s increase in straight-line velocity (95%CI: 0.06, 0.99), and a 0.60 m/s increase in average path velocity (95%CI: 0.04, 1.16). Additionally, GSH levels were associated with several sperm trajectory parameters including average lateral head displacement, average beat frequency, average movement angle, linearity, oscillation, and forward progression. The relationship between GSH levels and sperm quality parameters is detailed in .

**TABLE:3** Correlation between GSH in seminal plasma and sperm concentration, motility, movement velocity and trajectory

### 2.3 Relationship Between Energy Metabolism and Sperm Quality Parameters

The relationship between energy metabolism and semen quality parameters showed that ATP levels were correlated with multiple parameters including progressive sperm density, sperm motility, movement velocity, and trajectory. Each 1 nmol/mg protein increase in ATP was associated with a  $4.34 \times 10^6$  ml increase in progressive sperm density ( $95 \times 10^6$ ,  $6.68 \times 10^6$ ), a 6.26% increase in total motility (95%CI: 2.43%, 10.10%), a 4.65% increase in PR (95%CI: 1.41%, 7.88%), and a 1.62% increase in NP (95%CI: 0.65%, 2.59%). Additionally, each 1 nmol/mg protein increase in ATP was associated with a 4.73 m/s increase in curvilinear velocity (95%CI: 2.22, 7.25), a 3.11 m/s in-

crease in straight-line velocity (95%CI: 1.57, 4.65), and a 3.44 m/s increase in average path velocity (95%CI: 1.73, 5.15). Sperm trajectory parameters also changed significantly ().

**TABLE:4** Correlation between ATP level in sperm and sperm concentration, motility, movement velocity and trajectory

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## Discussion

In this study, we systematically investigated the effects of oxidative stress and energy metabolism on multiple sperm quality parameters in men. Consistent with our hypothesis, seminal MDA, GSH, and ATP levels were significantly associated with multiple parameters of sperm motility, movement velocity, and trajectory. While previous studies mainly explored the effects of oxidative stress and energy metabolism on sperm concentration and motility, our study systematically analyzed the associations between seminal oxidative stress and energy metabolism levels and more than 10 parameters including sperm density, motility, movement velocity, and trajectory. Our findings suggest that supplements reducing oxidative stress and enhancing energy metabolism could improve male sperm quality, providing epidemiological evidence for promoting male reproductive health.

Our study demonstrated that seminal MDA and GSH levels are associated with sperm motility, movement velocity, and trajectory changes. To our knowledge, MDA and GSH are major and most studied products of oxidative stress [18,20]. MDA is one of the most common products of polyunsaturated fatty acid peroxidation and has been widely used to evaluate oxidative stress levels [18], serving as a direct indicator of lipid peroxidation in seminal plasma [19]. Higher MDA levels represent more severe oxidative stress. Our results show that higher MDA levels are associated with lower sperm motility, decreased movement velocity, and adverse trajectory changes, demonstrating the detrimental effects of excessive oxidative stress on male reproductive health. Consistent with our study, several studies have reported significant associations between MDA and reduced sperm quality [19,21,22]. For example, a cross-sectional study of 346 men in Poland found that MDA levels were 12% higher in men with asthenozoospermia than in controls [21].

GSH is part of the non-enzymatic antioxidant defense system that protects lipids, proteins, and nucleic acids from oxidative damage [20]. Higher GSH levels indicate higher antioxidant capacity and lower oxidative stress status, and GSH has also been used as an important biomarker of reproductive health in some studies [23,24]. For instance, Atig et al. conducted a prospective study of 250 adult men and found that GSH levels were significantly higher in healthy men than in infertile patients. Additionally, they noted that GSH was significantly associated with total sperm motility and concentration [24]. Atig et al.'s results showed that higher GSH levels were associated with better sperm

quality and lower infertility risk, which is consistent with our findings. In summary, our study demonstrates that oxidative stress plays a crucial role in sperm quality and male reproductive health. Although the specific biological mechanisms by which oxidative stress affects sperm quality remain unclear, damage to sperm chromatin, peroxidation of sperm membranes, and increased sperm cell apoptosis cannot be ignored [25,26].

ATP is the primary energy source for sperm function [27-30]. Higher ATP levels are more conducive to sperm generating sufficient energy to overcome physical barriers in the female reproductive tract, reach the oocyte, and penetrate its zona pellucida [16]. Our results show that higher ATP levels are associated with higher sperm motility, increased movement velocity, and positive trajectory changes, indicating that energy metabolism significantly affects male sperm quality. Consistent with our study, Shan Dan et al. collected samples from 60 normozoospermic men and 50 men with asthenozoospermia and found that ATP content was significantly lower in the asthenozoospermia group ( $234.74 \pm 81.21$  mol/mg vs.  $437.38 \pm 142.54$  mol/mg) [31]. K. Jueraittibaiké et al. conducted a study investigating the effect of vitamin D on sperm motility and found that elevated ATP levels were significantly associated with increased sperm progressive motility [16]. Although the specific biological mechanisms by which ATP affects sperm quality remain unclear, some experiments have shown that decreased respiratory chain complex activity [32], reduced mitochondrial membrane potential [33-35], mitochondrial DNA alterations [36], and reactive oxygen species-induced mitochondrial damage [37,38] are key mechanisms.

To our knowledge, this is the first study to systematically evaluate the effects of oxidative stress and energy metabolism levels on multiple parameters including sperm density, motility, movement velocity, and trajectory. Our study provides a reference for comprehensively understanding the impact of oxidative stress and energy metabolism on male reproductive health. However, this study has several limitations. First, the participants were men of reproductive age visiting the hospital's reproductive medicine center. Although we selected first-visit patients for pre-pregnancy checkups, we could not completely exclude coexisting reproductive health problems, which may cause some deviation from the healthy population. Second, because outpatients undergoing semen analysis were unwilling to disclose more personal information, we could not collect data on participants' occupation, fertility status, and detailed lifestyle habits, which may have introduced some confounding factors. However, we adjusted for participants' age, education level, BMI, smoking status, alcohol consumption, and semen volume, and most results from the adjusted model were consistent with the crude model, indicating that our findings are robust. Third, this study only included 67 semen samples for oxidative stress detection and 42 samples for energy metabolism detection; future studies with larger sample sizes are needed to confirm our findings. Finally, this study used a cross-sectional design, which cannot establish causal relationships; future cohort studies are needed to validate our findings.

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## Conclusion

In summary, this study systematically evaluated the effects of oxidative stress and energy metabolism levels on multiple parameters of sperm motility, movement velocity, and trajectory. The study found that higher oxidative stress levels are associated with lower sperm motility, slower movement velocity, and adverse trajectory changes, while higher ATP levels are associated with increased sperm motility, faster movement velocity, and favorable trajectory changes. Given the increasingly serious problem of male reproductive health, this study suggests that supplements reducing oxidative stress and enhancing energy metabolism could improve male sperm quality, providing scientific evidence for precise intervention in male reproductive health and ensuring stable population growth.

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## Author Contributions

ZHAO Xiaolong was responsible for collecting and organizing medical records and writing the initial draft; NIU Zhiping organized medical records and analyzed data; TAN Jidong was responsible for organizing experimental results; HAN Donghui proposed the research direction; YANG Fa and WEN Weihong were responsible for revising the manuscript; WANG Anhui and QIN Weijun were responsible for quality control and review of the article and overall responsibility; all authors approved the final manuscript.

## Conflict of Interest

The authors declare no conflict of interest.

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