Original Article

The Role of Glutathione in Male Infertility

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ABSTRACT

Background: Numerous research studies have attempted to determine the causes of male infertility with the objective of developing therapeutic approaches to effectively improve various semen parameters. **Aim:** The presented intervention is a quantitative approach that categorically assesses the therapeutic advantage of oral GSH (glutathione) administration on various semen parameters including sperm concentration, morphology, and motility in infertile males. **Methods:** The prospective placebo-controlled study included 101 infertile adult males through random selection between the timeframe of Jan 2017 to Mar 2018. We selected total 101 subjects who did not experience any chronic disease of the reproductive system and exhibited normal female factor. GSH oral therapy was administered between 0 to 6 months, 51 patients received GSH therapy and 50 patients received placebo in the form of glucose sachets. At the time of 0, 3 and 6 months, the blood and semen samples were taken for analyses for treatment and placebo groups. **Results**: The findings recorded at 0 weeks, 3 months, and 6 months interval revealed a significant p-value. At 0 week, there wasn't any statistical significance for the results while at 3 months, GSH value was 4.55 mg/dl for GSH group therapy in comparison for 1.55 mg/dl for placebo group which was statistically significant. **Conclusion:** The study findings revealed a strong positive relationship between oral GSH therapy and the selected sperm parameters.

Key words: *Oral GSH, male infertility, glutathione, sperm concentration, sperm morphology, sperm motility.*

Male infertility is associated with the psychological trauma, specifically for married couples and poses a serious threat to their mental health and wellness to a considerable extent. Oxidative stress is one of the major causes of male infertility and substantially impacts the equilibrium between protective antioxidants and reactive oxygen species (ROS). Several antioxidants antagonize the adverse impact of reactive oxygen species while facilitating the cellular repair processes. Glutathione (GSH) effectively antagonizes the level of reactive oxygen species while effectively inducing the antioxidant defense mechanisms of the human body [1].

Antioxidant property of GSH also helps in controlling the level of free radicals in the context of stabilizing reproductive microenvironment. GSH, in this manner, is believed to improve the reproductive capacity of adult males. The study finding of Yao DF et al 2016, reveals the intracellular antioxidant action of GSH that effectively improves sperm morphology and motility in adult males [2]. The antioxidant genes including glutathione S-transferase (GST) and glutathione peroxidase (GPX) plays a pivotal role in normalizing the sperm function and spermatogenesis in males [3]. However, disruption of these genes substantially increases the risk of subfertility, oligozoospermia, oligoasthenoteratozoospermia, and reduced sperm quality [3].

The adverse impact of functional polymorphisms and reactive oxygen species on GST and GPX leads to the establishment of infertility pattern in the affected males.

GSH substantially improves mitochondrial DNA function and proves to be a co-factor for numerous vitamins and enzymes that effectively explores the impact of glutathione oral therapy on the sperm motility, morphology, and concentration in adult males [4]. Many previous studies have revealed the potential of use of GSH on sperm motility & morphology [5-9]. In fact, evidence-based findings reveal research gaps in relation to GSH therapy and enhancement of semen attributes in adult males.

Accordingly, the present study evaluates the effectiveness of GSH therapy in elevating the overall semen functionality and sperm count. It explores the potential of orally administered GSH in terms of improving the sperm motility, concentration, and morphology in adult males.

METHODS

The present prospective randomized placebo-controlled study was conducted in Saladin province of Samarra city (Iraq) between Jan 2017 to Mar 2018. The study deployed 51 infertile male subjects who exhibited normal female factor for the administration of oral glutathione (250mg sachets), for tenure of 6-months. However, 50 infertile males received the placebo treatment. The patients affected with chronic diseases including mumps, hydrocele, neoplasm, varicocele, trauma from prolonged riding, neoplasm, varicocele, vas deferens obstruction, hypospadias, and genital tract infection, were summarily excluded from the study. Furthermore, infertile males, who had recently received infertility treatment were also not allowed to participate in the research study. The male participants between the age group of 35-40 years, were included in the research intervention.

Informed consent was obtained from the entire study subjects while categorically explaining them the interventions, objectives, and outcomes. Data collection from study participants was undertaken after the acquisition of the informed consent. Oral administration of GSH sachets to the study participants (i.e. the treatment group only) was undertaken for a period of 6-months. The placebo group did not receive the GSH treatment for the same time. However, placebo group participants (who received glucose sachets), remained unaware of the treatment intervention because of the single-blinded nature of the study intervention.

Blood and semen samples were obtained from the treatment and placebo groups at 0 weeks, 3 months, and 6 months period. Blood sampling was performed with the core objective of detecting the GSH concentration. Addition of a precipitating solution and centrifugation were performed in the context of evaluating the seminal plasma GSH by utilizing the Ellman method. Data collection from study participants was undertaken and the participants shared the significant information related to their social habits, marriage duration, occupation, and age during the interview session.

Data analysis was done through SPSS 15.0 in the windows interface. Mann Whitney U-test and unpaired t-test were systematically utilized for assessing the data significance for P value<0.05. The genital organs of the entire study participants were examined to evaluate their size of vas deferens, epididymis, and testes while concomitantly assessing/ruling-out the presence of a varicocele.

RESULTS

Total 101 patients were included in this study and out of them 51 patients received GSH treatment. Table 1 present the outcomes obtained at 0 weeks, 3 months, and 6 months of oral GSH and placebo treatment administration.

Table – 1 (Participants' age and semen parameters recorded at 0-week)

Domains	Placebo group (n=50)	GSH group (n=51)	P value
Age (years)	35.82±4.92	35.21±5.18	> 0.05
Semen Volume (ml)	2.21±0.92	2.25±0.85	> 0.05
Semen concentration (million)	51.5±8.2	50.2±8.1	> 0.05
% of motility	27.5±2.5	27.0±2.6	> 0.05
Morphology	9.5±3.1	9.8±3.2	> 0.05

No significant difference regarding the semen parameters was recorded between the two groups at the beginning of the study intervention.

Table – 2 (Seminal plasma GSH levels & GSH levels in blood)

GSH Level in Seminal Plasma (mg/dl)						
6 months		3 months		0 weeks		P value
Placebo n=50	GSH group n=51	Placebo n=50	GSH group n=51	Placebo n=50	GSH group n=51	
1.52 (0.27-7.02)	4.58 (2.55-7.25)	1.55 (0.26-7.04)	4.55 (2.58-7.20)	1.58 (0.26-7.02)	1.52 (0.25-6.92)	<0.001
GSH levels in the blood						
14.78 (0.80-29.2)	15.25 (2.28-26.2)	14.8 (0.89-29.1)	15.2 (2.26-25.4)	14.8 (0.86-29.20)	14.5 (0.85-28.2)	>0.05

The outcomes reveal serum plasma GSH elevation in the treatment group at 3rd and 6th months of the oral GSH therapy. P-value was recorded to be less than 0.001 during this tenure. The outcomes at 0 weeks, 3 months, and 6 months did not reveal any significant difference between blood GSH levels of the treatment and placebo groups (Table 2).

Table – 3 (Semen parameters in response to the oral GSH/placebo therapy)

Parameters	6 months		3 months		P value
	Placebo n=50	GSH n=51	Placebo n=50	GSH n=51	
% of motility	3.5	38.4	3.5	38.2	0.01
% of morphology	4.6	27.2	4.5	26	0.03
% of sperm concentration	1.6	24.2	1.8	24	0.01

The following outcomes regarding the semen parameters were recorded after therapeutic administration of oral GSH to the treatment group: The significant p-value of 0.01 for the sperm motility was recorded at 3rd and 6th months of treatment for the GSH group; The significant p-value for the sperm morphology was recorded as 0.03 for the GSH group at 3rd and 6th months of oral GSH treatment; The significant p-value of 0.01 for the sperm concentration was recorded for the GSH group at 3rd and 6th months of oral GSH administration (Table 3).

The study outcomes revealed oral GSH therapy as an effective treatment for improving the pattern of sperm concentration, morphology, and motility of the selected subjects.

DISCUSSION

Male infertility is a direct outcome of inconsistencies in sperm morphology, motility, and concentration. Immature oocytes significantly lead to premature chromosome condensation across the sperm cell lines. The study by Ahmadi S et al. 2016 advocates the need for semen analysis in the context of evaluating motility, morphology, and concentration of the human sperms [5]. The reduction in antioxidant semen capacity substantially increases the risk of sperm abnormalities including oligoasthenoteratozoospermia, teratozoospermia (i.e. disfigured sperm morphology), asthenospermia (i.e. decreased sperm motility), and oligozoospermia (i.e. decreased sperm concentration) [5]. Since glutathione is one of the several antioxidants in human serum, its elevated concentration is believed to improve sperm physiology and concentration in adult males.

The study by Majzoub A et al. 2017 reveals the potential of GSH to effectively protect the human sperms from the adverse impact of lipid peroxidation [6]. This protective effect of GSH improves the sperm motility and viability to a considerable extent. Glutathione reductase extends protective effect over the sperm membrane attributes and tail-beat frequency. Some studies reveal the poor absorbance of GSH across the intestinal tract that reciprocally impacts its bioavailability and therapeutic outcomes [6]. Research intervention by Lombardo F et al. 2011 [7], reveals the limited evidence regarding the beneficial outcomes of antioxidant therapies in male affected with infertility. In-vitro assessment reveals the potential of GSH in terms of safeguarding the ROS-based

DNA loss in adult males. Similarly, the pre-clinical study by Tuncer et al. 2010 [8] reveals limited spermatic DNA damage under the impact of GSH administration. Study outcomes of Majzoub A et al. 2018 evidently describe the beneficial outcomes of several antioxidants on the male fertility pattern [9]. However, prospective studies require execution on a wider scale in the context of determining an optimal antioxidant therapy to facilitate the safe and effective treatment of male fertility in clinics and hospital settings

The study outcomes by Meybodi AH et al. 2012, [10] reveal the capacity of GSH intervention to reduce the oxidative stress of the sperm cells that resultantly improves their motility and increases the scope of fertilization. The outcomes of the presented study effectively concord with the evidence-based findings that reveal the protective effect of GSH on sperm motility and maturation. However, the presented study does not reveal the GSH mechanism that safeguards seminal plasma and sperm from oxidative stress. Previous studies also suggested about the higher risk of oxidative stress-based disruption of sperm cell line in the infertile males who reportedly undergo glutathione transferase enzyme mutation [10]. Numerous research studies reveal both positive and negative correlations (i.e. controversial findings) between the GPX activity in seminal plasma and sperm motility/quality pattern [11]. These outcomes substantiate the requirement of assessing the seminal plasma in the context of determining probable mutations in the antioxidative defense enzymes across the sperm cell lines. This diagnostic intervention is required to identify the defects or mutations in protein expressions that directly result in male infertility. Accordingly, researchers can optimize the oral GSH dosage to effectively overcome the inconsistencies in antioxidative defense enzyme for improving the overall semen quality. The presented study outcomes prove to be the ladder in this direction that the researchers need to utilize for evaluating numerous semen parameters on a wider scale to effectively generalize the utilization of GSH therapy for the infertile males.

The assessment by Agarwal et al. 2014 [12] reveals the potential of the excess residual cytoplasm of the deteriorated immature spermatozoa to disrupt the sperm morphology and motility. The excess residual cytoplasm of the degraded spermatozoa utilizes the hexose-monophosphate shunt to effectively induce the NADPH system. This resultantly hinders the ROS equilibrium and increases the oxidative stress that results in degradation of sperm quality and fertilization capacity of the adult males [12]. Our study reveals the positive influence of oral GSH therapy on sperm morphology. However, prospective research studies require execution with the objective of understanding the impact of oral GSH therapy on NADPH induction pattern across the deteriorated spermatozoa. This will effectively help in determining the biochemical pathways interfered by the oral GSH therapy in the infertile males.

The analysis by Hsieh et al. 2006 [13] reveals an insignificant correlation between seminal quality and GPX activity. Study outcomes advocate the need for assessing seminal MDA (malondialdehyde) concentration to identify the extent of degradation in sperm motility and concentration in the infertile males. This study effectively reveals a positive correlation between the sperm concentration and oral GSH administration. However, the study does not identify the mechanism of GSH interaction with seminal malondialdehyde in the study subjects. The assessment by Yesteet al 2013 [14] reveals the constructive influence of reduced-glutathione on the nucleoprotein pattern of the deteriorated and underdeveloped spermatozoa. The findings, therefore, indicate the need for GSH administration for the enhancement of sperm viability in the infertile males. Our study indicates the linear improvement in semen parameters following the GSH administration. However, greater analysis of the associated mechanisms is required to authenticate and generalize the positive correlation between oral GSH therapy and extended semen parameters and biomolecular pathways.

The study limitations are based on the restricted sample size and absence of a thorough analysis of biochemical interactions of GSH with the deteriorated sperm cells of the selected males. The researchers need to replicate the study on a wider scale while considering the oral absorption and bioavailability of the oral GSH in the male population. The prospective assessment of GSH effects on various semen parameters including MDA concentration, NADPH system, glutathione peroxidase activity, sperm nucleus structure, and GSHr/GSSG concentration is necessarily required to effectively optimize oral GSH therapy for the infertile males. Furthermore, GSH impact on ROS and oxidative stress requires further exploration

while evaluating the associated biomolecular pathways. The researchers also need to investigate the scope of co-administering other antioxidants like carnitine, selenium, and vitamin B complex with oral GSH therapy to minimize the prevalence of male infertility in the selected population.

CONCLUSION

The present study effectively evaluates the effectiveness of oral GSH therapy on semen parameters including sperm motility, morphology, and concentration. The findings categorically reveal the therapeutic advantage of oral GSH intervention in terms of improving the selected semen parameters in the infertile males.

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