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The effect of selenium therapy on semen parameters in infertile men with varicocele

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Abstract

Oxidative stress and varicocele have been linked to male infertility. The aim of this study was to assess the effect of selenium therapy on semen parameters in infertile men with varicocele. Forty infertile men with varicocele (Group 1) and forty infertile men without varicocele (Controls, Group 2) with oligoasthenospermia who fulfilled the selection criteria were included in the study. All participants received selenium (200 µg/day) orally for three months. Seminal fluid analysis (WHO 5th criteria) was performed at baseline and after three months of selenium treatment. The results were compared between groups before and after therapy. Following three months of selenium therapy, sperm progressive motility significantly increased in patients with and without varicocele ($P<0.01$, $P<0.05$ respectively; 32.7% change vs. 24.1% respectively) but the improvement was higher in patients with varicocele. Similarly, sperm total motility significantly increased in patients with and without varicocele ($P<0.01$, $P<0.05$ respectively; 23.6% change vs. 12.6% respectively) and the increment was higher in infertile men with varicocele. Sperm concentration and normal sperm morphology; however, did not significantly change before and after selenium therapy. In conclusion, treatment of infertile men with varicocele and oligoasthenospermia with selenium (200 µg/day) for 3 months improves sperm progressive and total motility and the increment is higher than in infertile men without varicocele. Thus, selenium could be an adjuvant treatment for varicocele-associated male infertility.

Keywords: selenium, male infertility, varicocele, semen

1. Introduction

Infertility is a global health issue affecting 8-15% of couples and approximately 48 million individuals worldwide with medical, psychological, and financial consequences (1). Infertility is diagnosed when the couple fails to conceive after twelve months of regular unprotected intercourse. Male factor accounts for approximately half of infertility cases. The underlying causes of male infertility encompass a wide range of conditions including undescended testis, varicocele, infections, endocrinopathies, systemic diseases, testicular tumors, radiotherapy, chemotherapy, immunological, genetic, and environmental factors (2–4). Reduced semen parameters are defined as sperm concentration below 15 million/ml, sperm progressive motility below 32%, total motility below 40%, and normal sperm morphology below 4% according to WHO 2010 5th criteria (5). A combination of low sperm concentration and motility is known as oligoasthenospermia (OA).

Varicocele is a condition characterized by the enlargement of veins within the scrotum. Varicocele has been found in 15% of fertile men but the prevalence among infertile men is approximately 40%(6). Several studies have demonstrated an association between varicocele and altered semen parameters(7,8). Varicocele is associated with decreased sperm concentration, motility, and morphology. These alterations could be attributed to increased scrotal temperature, hypoxia, venous stasis, accumulation of toxic metabolites, and elevated levels of reactive oxygen species (ROS) in semen, leading to oxidative stress (OS), sperm DNA damage (SDF), and impaired fertility (8,9). Varicocele may also have detrimental effects on ART outcomes(10).

OS is the result of prooxidants/antioxidants imbalance. A variety of antioxidant medications have been tried to treat OS and SDF and resulted in a reduction of ROS, lower SDF levels, and improvement in semen parameters and seminal antioxidant markers (11). However, antioxidant therapy is limited by the lack of consensus on a standardized treatment regimen including the type, dose, and duration of antioxidant therapy.

Selenium is an essential micronutrient that plays a key role in male reproduction including testosterone metabolism and sperm selenoproteins (12). Selenium also plays structural and enzymatic roles and is also a cofactor for many enzymes involved in antioxidant, anti-inflammatory, endocrine, immune modulation, DNA, and RNA synthesis (13). Sperm selenoproteins also maintain sperm structural integrity and glutathione peroxidase (GPx) antioxidant activity against ROS. Specifically, GPX4 has been found in the sperm nucleus where it performs stabilization of the condensed chromatin during spermatogenesis (14). Studies have reported decreased selenium levels in infertile men and that selenium therapy was associated with increased semen parameters (14,15). Therefore, this study aimed to explore the impact of selenium on semen parameters in infertile men with varicocele after three months of treatment as compared to the infertile men

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without varicocele.

2. Materials and Methods

2.1. Patients

In this prospective controlled clinical study, 40 infertile men with varicocele and OA (Group 1) were recruited from Infertility Clinic Babylon, Iraq from April to July 2023. Varicocele was diagnosed by scrotal examination in upright positions before and during Valsalva's maneuver and was confirmed by Doppler sonography. The control group (Group 2) consisted of 40 infertile men without varicocele and have OA. Participants with other known predisposing factors for male infertility such as undescended testicles, endocrinopathies, systemic diseases, genital infection, smoking, alcoholism, and recent antioxidants intake were excluded.

Seminal fluid analysis (WHO 2010 5th criteria) was performed at baseline and after 3 months (5) . All patients received selenium (America Medic & Science, Washington USA) 200 µg/day orally for 3 months. The selenium dose adopted in this study was used previously (14). Semen parameters were compared between the two groups at baseline and after three months of selenium therapy. Ethical approval was issued by the University of Babylon and informed consent was received before the start of the study.

2.2. Semen analysis

All the patients were asked to refrain from sexual activity for two to three days before the collection of the semen sample. The collection of semen samples was achieved by masturbation and the patients were instructed to provide a complete sample. Following collection, the semen sample was held at 37°C for liquefaction and then analyzed according to WHO 2010 5th criteria for all semen parameters (5). All the analyses were undertaken by the same investigator and for all participants, two semen samples were assessed at baseline and after three months, and their average value was used for this study.

2.3. Statistical analysis

Data analysis was performed with MedCalc software (v.22). Data normality was assessed with Kolmogorov–Smirnov test. The results were expressed as mean ± SD. Paired t-test was used to compare the results before and after selenium therapy in each group. The magnitude of change in semen parameters was expressed as percentage. P<0.05 was considered statistically significant.

3. Results

The mean age for patients in groups 1 and 2 was 34.3± 9.2 and 32.4±11.5 years respectively (Table 1). The mean for duration of infertility in groups 1 and 2 was 7.3±6.2 and 6.4±4.9 years respectively. After three months of selenium therapy, patients with varicocele and without varicocele demonstrated significant increment in sperm progressive motility but the improvement was significantly higher in patients with varicocele (P<0.01, P<0.05 respectively; 32.7% change vs. 24.1%) (Table 1 and fig. 1). Similarly, total sperm motility significantly increased in both groups but the increment was significantly higher in patients with varicocele as compared to those without varicocele (P<0.01, P<0.05 respectively; 23.6% change vs. 12.6%).

Table 1. Patients characteristics and semen parameters before and after selenium therapy

	Patients with varicocele (n=40)			Patient without varicocele (n=40)		
Age	34.3± 9.2		% Change	32.4±11.5		% Change
Duration of infertility (years)	7.3±6.2			6.4±4.9		
Concentration (million/ml)	7.8±2.6	9.1±3.5	16.6%	7.4±2.9	8.8± 4.1	18.9%
Progressive motility (%)	16.8±7.6	22.3±8.5**	32.7%	18.6±8.2	23.1±7.8*	24.1%
Total Motility (%)	21.6±6.9	26.7±6.5**	23.6%	23±6.2	25.9±6.8*	12.6%
Normal morphology (%)	8.5±4.2	10.7± 6.4	14.1%	7.8±3.3	8.5± 4.1	8.9%

* P<0.05 as compared to baseline
** P<0.01 as compared to baseline

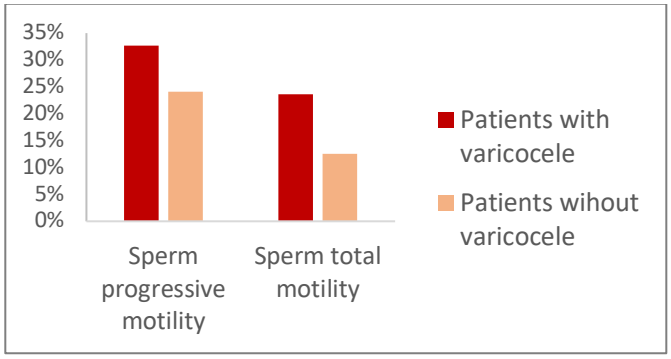

Fig. 1. Percentage change in sperm motility patient with and without varicocele after selenium treatment

4. Discussion

Recent years have witnessed advances in the management of infertile men including sperm function tests, sperm retrieval, and sperm selection techniques for ART treatment. Further, several studies have tried different oral antioxidants to treat men with idiopathic male infertility but with inconsistent results. Recently, systematic reviews and a meta-analysis by our group and other colleagues have also illustrated the beneficial effects of oral antioxidants on semen measures. However, there is no standardized treatment regimen. Surgery is the main therapy for varicocele but other modalities of treatment including antioxidants have been also tried. The

WHO 2010 5th criteria for semen analysis were used to define seminal fluid abnormalities. While conventional semen analysis is the standard initial assessment method for male infertility worldwide, semen analysis has many limitations. The main drawbacks stem from the fact that the reference values of semen analysis in the WHO manual were obtained from fertile rather than infertile. Another limitation is the adoption of the 5th centile as a cut-off value to distinguish fertile from infertile men while there is an overlapping of the values of semen parameters between fertile and infertile subjects (16). In addition, semen analysis cannot assess sperm function and also has geographical, genetic, and ethnic variations (17).

The current study results are in agreement with previous studies which illustrated higher semen measures following oral antioxidant therapy (18–20). Moslemi and Tavanbakhsh explored the impact of selenium (200 µg/day) in combination with vitamin E (400 units) for 100 days in infertile patients with idiopathic asthenoteratospermia and showed increased sperm motility and morphology post-therapy (21). This increment was attributed to the reduction in intracellular anion superoxide and sperm apoptosis. Further, in our previous study, a comparison was made for the effect of selenium (200 µg/day) with coenzyme Q10 (200 mg/day) in patients with idiopathic oligoasthenoteratospermia for three months in patients with idiopathic male infertility and demonstrated increased sperm concentration, motility, and seminal antioxidant markers in both groups although coenzyme Q10 produced higher increment (15). In one study; however, the administration of selenium (300 µg/day) for 48 weeks produced no significant changes in semen parameters (22). In addition, a high dose of selenium may produce detrimental effects on semen parameters (23).

Other studies have explored selenium therapy in combination with other antioxidants and illustrated variable beneficial effects on one or more semen parameters (24–26). It is essential to mention that combined antioxidant formulations in these studies have a wide range of selenium doses ranging from 10 to 225 µg (19). This fact in association with the heterogeneity of study design, type, dose, duration of treatment, and patient group makes the comparison more challenging. Higher semen measures detected post-selenium therapy in the present study could be due to the antioxidant properties of selenium, upregulation of GPx activity, reduction of OS, and the role of selenoproteins in sperm function (27). These improvements could be also explained by the recent observations of anti-inflammatory, endocrine, sperm mitochondrial membrane potential, genetic, and immune modulation effects for selenium that affect male fertility potential (13,23).

In the current study, selenium therapy in infertile men with varicocele and OA resulted in increased sperm motility which was higher than in those without varicocele. Our findings are congruent with other studies that demonstrated improved semen parameters in infertile men with varicocele following different regimens of antioxidant therapy (6,28). In a controlled study that assessed the effect of micronized purified flavonoid fraction in patients with painful varicocele, improvement in all semen parameters following 6 months of therapy was reported (29). However, treatment with pentoxifylline with zinc and folic acid (for 12 weeks) in men with varicocele-related infertility resulted in increased normal sperm morphology only (30). Studies on the effect of selenium on semen parameters in infertile men with varicocele are scarce. Oral selenium therapy in normal and varicocelized rats was associated with increased antioxidant capacity and reduced damage to testicular architecture (31). Another study illustrated improved testicular biochemical and morphological parameters in rats with experimental varicocele after lycopene and selenium therapy (32)

It is essential to mention that studies which have explored the impact of selenium on seminal SDF are scarce and many previous studies have investigated selenium in combination with other micronutrients. In addition, previous studies were heterogeneous, and various doses and durations of treatment were used in patients with one or more seminal abnormalities. This heterogeneity makes a direct head-to-head comparison of the findings and the impact of antioxidant therapy on male fertility challenging.

Previous studies that explored the impact of antioxidant therapy on semen measures in infertile men also illustrated different study designs. Some of these studies were before and after studies while the others were controlled trials. It is worth mentioning that a variety of antioxidant therapy were used in these studies either as monotherapy or a combination of various antioxidants. A lack of consensus on the dose of antioxidants was also demonstrated in these clinical studies. A variation in dietary intake for each patient could also affect the results of these studies. Some of these studies considered dietary intake using various questionnaires while others did not include dietary assessment in their design. Dietary assessment; however, could be influenced by recall bias as well as the complex interaction between different dietary constituents. The parameters measured were also different in these studies. Some studies explored the effect of antioxidants on semen measures only while others have additionally assessed OS markers or sperm DNA fragmentation. Using different primary endpoints in different clinical studies makes a direct comparison of these studies more difficult.

Limitations of the current study include a small number of participants (which is due to consent issues) and a lack of dietary assessment of selenium intake. Also, the results of the present study may not be generalizable to all areas as it was performed in a single location.

Treatment of infertile patients with varicocele and OA with selenium (200 µg/day) for 3 months improves sperm

progressive and total motility and the increment was higher than in infertile men without varicocele. Thus, selenium could be an adjuvant treatment for varicocele-associated male infertility.

Conflict of interest

The authors declared no conflict of interest.

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None to declare.

Authors' contributions

Concept: A.T.A., Design: A.T.A., Data Collection or Processing: A.T.A., Analysis or Interpretation: A.T.A., Literature Search: A.T.A., Writing: A.T.A.,

Ethical Statement

Approval was obtained from University by Babylon Ethics Committee, the study started. The ethics committee decisions is EC/12-2023.

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