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ORIGINAL PAPER

Therapeutic supplementation with antioxidants and vitamins improved sperm motility among infertile men with idiopathic low spermatogenesis

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Summary ***Background: Spermatogenesis is worsened by reactive oxygen species (ROS) and antioxidants could reduce ROS induced sperm damage.***
Methods: This prospective cohort study evaluated the potential therapeutic effects of a combination of vitamins, minerals and antioxidants on the sperm quality parameters of infertile men with idiopathic low spermatogenesis. Seminal fluid analysis tests were performed before treatment, 3 and 6 months after treatment.
Results: The treatment resulted in a significant improvement in the rate (%) of sperm motility from 16.95 ± 6.93 to 23.11 ± 8.87, after 3 months and reached 23.68 ± 8.73 after 6 months (p = 0.0006) whereas a non-significant increase in sperm count (from 13.05 ± 8.1 to 15.79 ± 7.9 after 3 months and 15.26 ± 10.3 million/ml after 6 months (p = 0.1650). Morphology and agglutination showed little changes. A positive correlation between sperm count and motility was observed after 3 months of treatment (r = 0.594; p = 0.007).
Conclusions: The combination of vitamins and antioxidants improved the sperm motility significantly and to a lesser extent the sperm count, however, sperm morphology and agglutination remained relatively unchanged. Using antioxidants is safe and can improve semen parameters.

KEY WORDS: *Infertility; Antioxidant; Sperm motility; Coenzyme Q10, L-carnitine; Zinc.*

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INTRODUCTION

Male infertility is generally defined as failure to conceive despite frequent, unprotected sexual intercourse for more than one year (1). Several theories behind male infertility have been proposed, including sperm disorders such as immature, abnormally shaped or non-motile sperm or presence of structural abnormalities that blocks the sperm pathway and stop the flow of semen. Male infertility may be the result of a genetic or birth defect (2), or other non-specific factors such as erectile dysfunction or chronic diseases. Besides these causes, other unknown causes are called idiopathic male infertility (3).

Male infertility affects 14% of couples worldwide. The prevalence varies between developed and underdeveloped countries, being higher in the latter, in which limited diagnosis and treatment resources exist (4, 5).

Nowadays, oxidative stress is accepted as a main contributing factor that impairs both sperm quality and quantity. Excess production of *reactive oxygen species* (ROS) or free oxygen radicals that cannot be efficiently scavenged by the antioxidant system can reduce sperm quality and quantity and impact male fertility (5).

Most of the energy produced by normal cellular aerobic metabolism requires oxidation in the mitochondria where the enzymatic reactions produce energy and ROS (as a byproduct). Sperm production may be affected by the amounts of released ROS. A free radical is normally an oxygen molecule containing one or more unpaired electrons. Oxygen molecules usually have two unpaired electrons, and this electronic structure makes oxygen more susceptible to radical formation (6-8).

In theory, using antioxidant medication may reduce these free radicals, consequently improving spermiogram metrics. In spite of many conclusive meta analysis, systematic reviews and reports including normal and infertile men, there are still no conclusive clinical data for using combination of antioxidants, vitamins and minerals together to improve seminal parameters in idiopathic male infertility.

The aim of the present study is to evaluate the potential therapeutic effects of antioxidants (*Coenzyme Q10, L-carnitine, citric acid, selenium, zinc, Ginseng*) and vitamins (B12, B7, B9, C, D, E) on sperm parameters among idiopathic infertile men with low spermatogenesis.

MATERIALS AND METHODS

Our study is a prospective cohort clinical study based on a selection of infertile men with idiopathic low spermatogenesis. The study compared sperm parameters before, during and after treatment with antioxidants, minerals and vitamins.

The inclusion criteria were men with at least one abnormal sperm parameter (count, motility, morphology, or

agglutination), aged between 25 and 40 years old, and without chronic medical illness or any known cause for infertility (including varicocele).
The exclusion criteria comprised men diagnosed to have varicocele or other fertility-related diseases (medical or surgical), a history of inguinal or scrotal surgeries, abnormal hormonal parameters, and individuals on anti-psychiatric or anti-depressant medications.
Vitamins, minerals and antioxidants were chosen based on previous reports claiming either the role of their individual deficiency in the pathogenesis of male infertility or suggesting the role of their individual supplementation in improving spermiogram parameters.
The included patients underwent one daily medical treatment with commercially available oral capsules offering a combination of vitamin B12 (75 µg), C (90 mg), D (15 µg), E (30 mg), folic acid (400 µg), biotin (150 µg), selenium (150 µg), zinc (15 gm), coenzyme Q10 (20 mg), L-carnitine (50 mg), citric acid (50 mg), and Siberian Ginseng Extract (30 mg).
Seminal fluid analysis tests were performed before treatment (zero time), during treatment (3 months) and after treatment (6 months). Spermiogram was performed after 3 to 5 days of abstinence; samples were collected in sterile containers in a laboratory and processed within 30 min of collection. Any sample less than 1.5 mL was discarded and recollected 3 days later. Results were obtained using a high-power field microscope, which took 4 to 6 hours. The WHO 2010 criteria were applied as the reference range (9). The counts in millions/mL, the percentage of motility and the percentage of normal forms were evaluated.
Normality tests and descriptive statistics were done before repeated measure ANOVA. Correlation between count, motility and morphology was performed for each time (zero time, 3 months and 6 months)
The agglutination was graded (Grade 0 = no agglutination; Grade 1 < 10 sperms per agglutination; Grade 2 = 10-50 sperm per agglutination; Grade 3 > 50 sperm per agglutination and Grade 4 agglutination of all the spermatozoa). Chi-square test was performed. All statistical analyses were used using GraphPad PRISM 8.

Results

Between July 2023 and June 2024, 25 patients met our inclusion criteria and were enrolled in the study. However, only 19 completed the 6 month follow up period. The data of 19 participants in the study were compared from day zero (the day before treatment started) to 3 months and 6 months after treatment. We found a notable increase in sperm counts after 3 months of treatment (15.79 ± 7.9 million/ml) versus the mean sperm count at baseline (13.05 ± 8.11 million/mL). The sperm counts reached (15.26 ± 10.31 million/ml) after 6 months (greater than at zero time but less than after 3 months of treatment). Repeated measures ANOVA was not significant for treatment ($p = 0.165$) but was significant ($p < 0.0001$) for raw factor (individuals) as in Figure 1.
The treatment with vitamins and antioxidants showed a notable improvement of sperm motility which was significantly increased up to 23.11 ± 8.87% (3 months) and to 23.58 ± 8.86% (after 6 months) compared to values before treatment (16.95 ± 6.93%). Repeated measures ANOVA ($p = 0.0007$) and Bonferroni's multiple comparisons tests were significant (see Figure 1).
Rate of sperm normal morphology increased after 3 months to reach (6.842 ± 7.426%) versus zero time (5.895 ± 5.16 %) but the increment did not reach the lowest level of significance ($p > 0.05$). Moreover, no further improvement was noticed after 6 months (6.84 ± 6.83%). The nonparametric Friedman repeated measures ANOVA test was not significant ($p > 0.05$).
The agglutination test showed no differences after 3 and 6 months of treatment (see Figure 1).
Interestingly, there was a notable correlation between sperm count and both motility and morphology which changed after treatment. Before treatment (zero time), a positive weak correlation between sperm count and motility ($r = 0.33$) or morphology ($r = 0.1$) and a very weak negative correlation between motility and morphology ($r = -0.09$) existed (see Figure 2). Correlation P values were > 0.05.
However, after 3 months of treatment; the correlation between sperm count and motility changed to be moderate and significant ($r = 0.594$; $p = 0.007$) which may reflect improvement in the spermatogenesis process yielding more sperms with improved function (motility). Regarding morphology, it was still negatively correlated to motility ($r = -0.276$). However, the correlation between morphology and count became negative ($r = -0.116$), figure 2. The p values of correlation were greater than 0.05.
After 6 months of treatment, the positive correlation between count and motility decreased to ($r = 0.4$). The correlation between morphology and motility was still negative ($r = -0.273$) but the correlation between morphology and count changed to a very weak positive correlation ($r = 0.083$) (see Figure 2).

Discussion

The present study showed a significant improvement of sperm motility after treatment with vitamins (B12, D, C, E, Folic acid and biotin), minerals (Zinc and selenium) and antioxidants (Coenzyme Q10, L-carnitine, citric acid, Siberian Ginseng Extract). Other parameters, such as count and morphology, were improved but the statistical results did not reach the lowest level of significance, also the improvement after 6 months was not superior (in most instances) to 3 months duration.
Interestingly, the correlation between count and motility improved to be significant and positive after 3 months of treatment. This may point to improvement in spermatogenesis process, increasing count and function. The negative correlation observed between morphology and motility before treatment did not improve with treatment even after 6 months. However, the correlation between count and morphology turned to positive after 6 months of treatment (compared to the negative correlation after 3 months).
Our hypothesis regarding sperm motility and the improved correlation between count and motility is that treatment with vitamins, minerals and antioxidants could improve sperm motility, possibly by scavenging ROS and

Figure 1.
Results of agglutination tests and Five point summaries and box-plots showing the results of spermiogram (sperm motility, morphology and count) before treatment (zero time), after 3 and 6 months of treatment.
P values of Chi-square test and repeated measure ANOVA and Bonferoni multiple comparisons are shown.

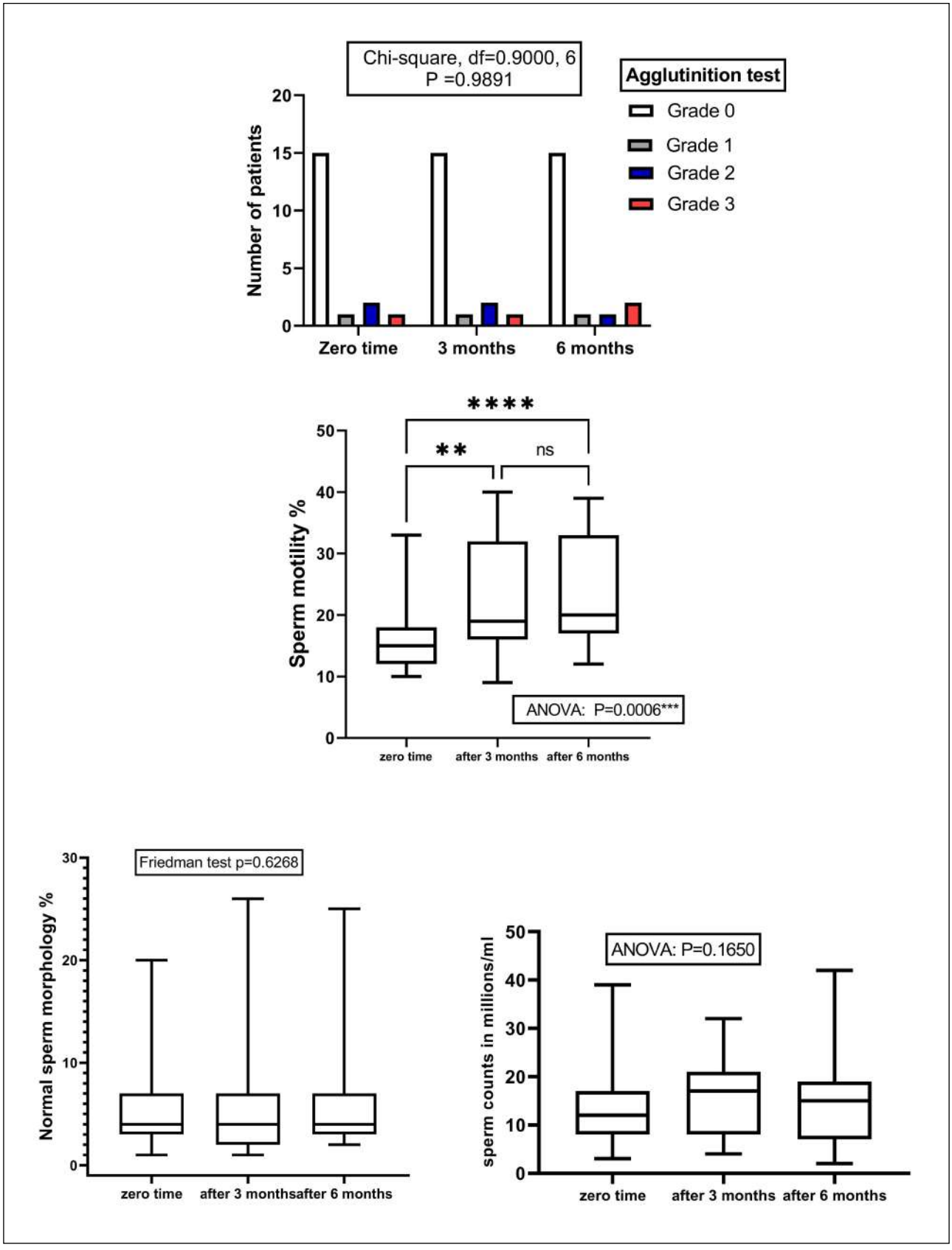
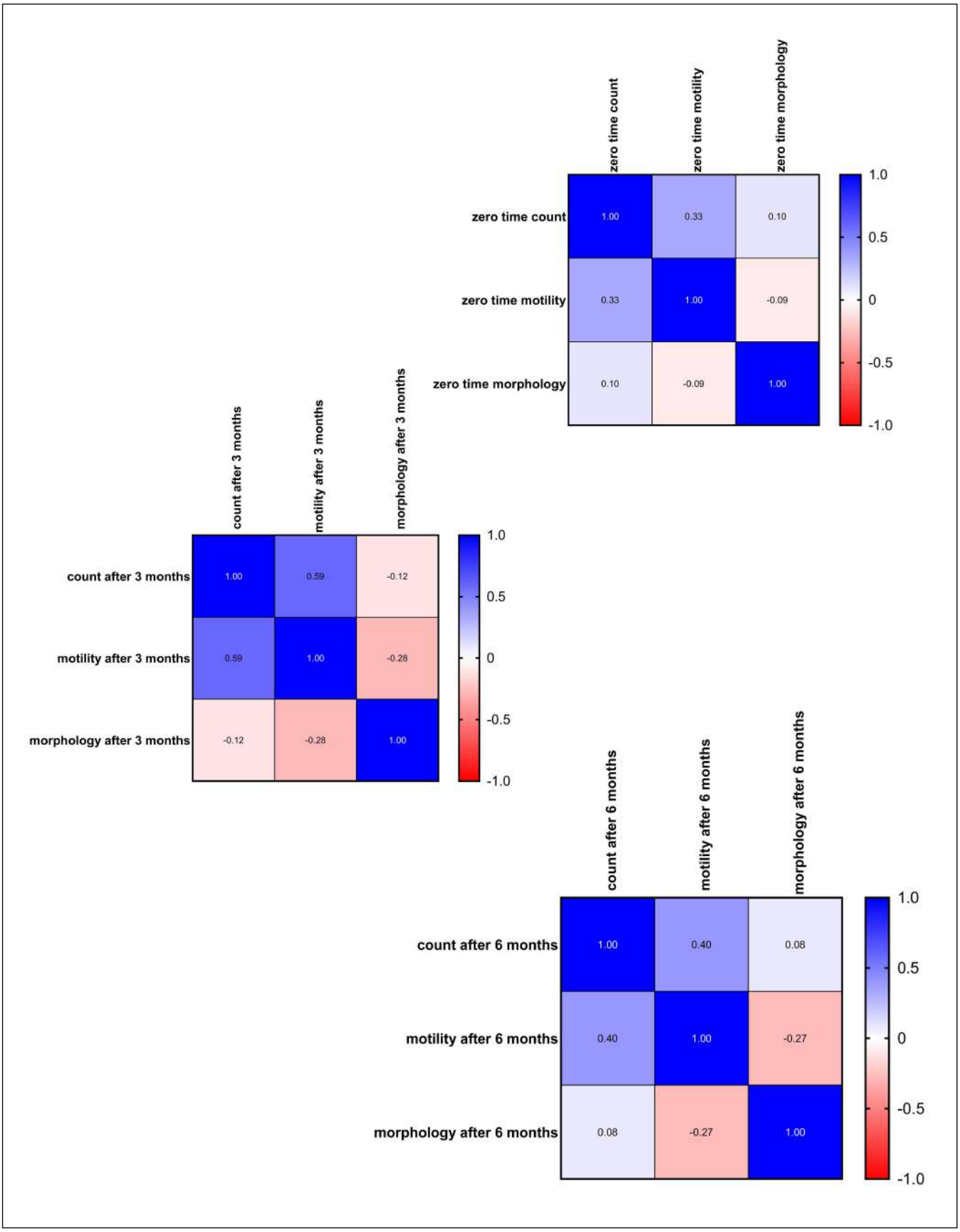


Figure 2.
Pearson's correlations between spermiogram parameters (sperm motility, morphology and count) before treatment (zero time), after 3 and 6 months of treatment.



improving cellular micro-organelles improving spermatogenesis especially at the first 3 months of treatment (but not after 6 months). We can't exclude the development of pharmacological tolerance to the effects of antioxidants through the continuous 6 month period of therapy. Further studies with intermittent therapy with antioxidants can confirm or reject such hypothesis.
Regarding sperm morphology, and the correlation between count and morphology, the effects of antioxidants may need 6 months of treatment to obtain a change, however, the nonsignificant results were a major limitation for proving the second part of our hypothesis.
Different reviews, meta analysis and systematic reviews in the literature emphasized the improvement of semen parameters by antioxidants among infertile men (10-12). The presents pilot study offered a clinical confirmation of the benefit of combined vitamins, minerals and antioxidants on sperm parameters among infertile men with idiopathic low spermatogenesis.
Recently, *Ibitoye et al.* studied the correlations of spermiogram parameters among normal population (13) and concluded that sperm count affected their morphology which in turn affected their motility. The findings of the present study showed that sperm count affected morphology positively (at zero time and after 6 months of treatment) but not after 3 months. However, there was a negative (but not significant) correlation between normal morphology and motility across the study. Our explanation for such conflict could be due to the nature of the included patients in whom the motility could be affected by physiological factors in the spermatozoa rather than their anatomical morphology. So, treatment with antioxidants, minerals and vitamins significantly improved motility with a significant positive correlation with count (but not with morphology).
Today, oxidative stress is accepted as a key factor in sperm quality and quantity due to the production of free oxygen radicals. The antioxidant system cannot control excess reactive oxygen species and, thus, potentially affect male fertility and reduce sperm quality and quantity (14-16). *Yves Menezo et al.* (17) reported that increased oxidative stress significantly reduced and impaired spermatogenesis. Therefore, antioxidant use may lower DNA repair burden and reduce oxidative stress-linked DNA damage to sperm. They also reported that antioxidants and vitamins are often given haphazardly, reducing efficiency or potentially causing detrimental effects. In the present study, changes in the most important spermiogram parameters were studied following the use of combination of important minerals, vitamins and antioxidants (not haphazardly) and the best improvement was in motility, and the best duration was 3 months.
Cardoso et al. studied the sperm parameters after antioxidant use and concluded that antioxidants protected against ROS, and may positively affect semen parameters, although a wider investigation is still restricted by practical limitations (18). *Meanwhile, Rajeev Kumar et al.* and *Kumar* and *Singh* did not find any improvement following antioxidant use for idiopathic male infertility, and their conclusions on drug therapy for idiopathic male infertility are empirical at best: there was no apparent benefit by using any medication in these patients (19, 20).
The role of vitamin E (powerful antioxidant) in pathogenesis of male infertility was documented by observing significantly lower levels of vitamin E and lower antioxidant capacity in seminal fluids of infertile men versus fertile individuals (21).
The motility of spermatozoa was positively correlated with serum folic acid (22). In parallel, the levels of vitamin B12 levels impacted significantly on sperm count, motility and morphology. Supplementation with vitamin B12 could decrease DNA damage and ROS production in sperms, leading to an increase in both sperm count and motility (23-25).
Reports explaining the exact role of vitamin D deficiency/vitamin D supplementation in male infertility pathogenesis/treatment are in favor of its potential deficiency among infertile men and its therapeutic potentials to improve sperm quality (25-29).
Recently, *Aris Kaltsas* discussed the crucial role of vitamins (B12, C, D, E, folic acid, biotin), minerals (selenium and zinc) & antioxidants (coenzyme Q10, L-carnitine, citric acid) on semen parameters and concluded that these antioxidants, individually or synergistically, can enhance sperm health and reproductive outcomes (30). The results of the present study showed a significant improvement in motility of sperms by using these vitamins, antioxidants and minerals together.

Conclusions

In conclusion, the findings of the present study suggest a significant positive impact of combined therapeutic supplementation of vitamins (B12, C, D, E, folic acid, biotin), minerals (*Selenium and zinc*), antioxidants (*Coenzyme Q10, L-carnitine, citric acid*) and Ginseng on sperm motility, whereas sperm count showed a non-significant increasing tendency. Across the study period, morphology remained relatively stable. Using antioxidants is safe and could improve semen parameters secondary to reducing oxidant stress, which may enhance fertility. The ideal duration of treatment is 3 months.

Declarations

Funding: *This research received no external funding.*

Institutional Review Board Statement: *The study proposal was approved by the institutional ethics committee (Faculty of Medicine Ethics Committee - Mutah University) and was performed in compliance with Good Clinical Practice and following the Declaration of Helsinki.*

Availability of data and material: *The data supporting this study's findings are available from the corresponding author upon reasonable request.*

Competing interests: *The authors declare no conflict of interest.*

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