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Improvement of Semen Quality in Idiopathic Infertile Men by Dietary Supplementation with TetraSOD®: A Pilot Clinical Trial

Juan Manuel Corral[1], Meritxell Jodar[2], Roger Matheu[1], Eva González[3], Enrique Castaño[4], Carlos Unamunzaga[4], Lalia Mantecón[4] and Carlos Infante[4]*

[1]*Urology Service, Andrology Unit and Clinical Institute of Nephrology and Urology (ICNU) of the Hospital Clinic Barcelona, Spain*

[2]*Molecular Biology of Reproduction and Development Research Group, Fundació Recerca Clínic Barcelona- IDIBAPS, Genetics Unit, Department of Biomedicine, Universitat de Barcelona (UB), Spain*

[3]*Fertypharm, 1 Sant Martí de l'Erm, Barcelona, Spain*

[4]*Fitoplancton Marino SL, Dársena comercial s/n, El Puerto de Santa María, Cádiz, Spain*

***Corresponding author:** Carlos Infante, Fitoplancton Marino SL, El Puerto de Santa María, Cádiz, Spain

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ABSTRACT

A randomized double-blind pilot trial was carried out to assess the potential beneficial effects of TetraSOD® on the semen quality of idiopathic infertile men. Forty individuals were recruited and divided into two experimental groups, receiving either 25 mg/day or 250 mg/day of TetraSOD® for 90 days. Semen volume, sperm concentration, total sperm number, progressive motility, and normal forms were determined both at the commencement (t=0) and the end (t=3 months) of the trial. Statistically significant increases in all parameters but normal forms were induced by the highest dose of TetraSOD®, revealing the potential use of this ingredient in the clinical treatment of idiopathic infertility in men.

Keywords: TetraSOD®; *Tetraselmis chuii*; Microalgae; Idiopathic Infertility; Semen Quality; Antioxidant

Abbreviations: CAT: Catalase; GPx: Glutathione Peroxidase; LRL: Lower Reference Limit; OS: Oxidative Stress; ROS: Reactive Oxygen Species; SOD: Superoxide Dismutase; WHO: World Health Organization

Introduction

Infertility can be defined as the failure to achieve a clinical pregnancy after 12 months of regular intercourse in the absence of any contraceptive measure [1]. The World Health Organization (WHO) has estimated that about 50-80 million reproductive-aged couples are affected worldwide by infertility, with male factors representing approximately 50% of all cases, either alone (30%) or in association (20%) with a female factor [2]. In men, idiopathic infertility represents around 30% of infertility cases, in which no obvious cause can explain the altered sperm characteristics these individuals exhibit [3]. Although infertile men are typically addressed to assisted reproduction techniques, alternative therapies and treatments have been considered to improve live-birth rates. It is nowadays accepted that the overproduction of Reactive Oxygen Species (ROS) during aerobic metabolism, or a deficiency in the cellular antioxidant mechanisms involved in the scavenging of ROS, can lead to an imbalanced state called Oxidative stress (OS). A range

of different environmental factors such as UV radiation, heavy metals, or pollutants, as well as alcohol or drug consumption, may help to provoke OS in cells [4]. It is well known that OS can cause damage to key cellular structures such as proteins, lipids, carbohydrates, and nucleic acids, and can be responsible for the induction of a range of health challenges and diseases [5]. Particularly, OS has been related to significant impairments during spermatogenesis, epididymal maturation, and sperm capacitation [6]. In addition, OS has an impact on seminal parameters, being negatively correlated with sperm count, function, and motility [7]. In this scenario, a positive impact on sperm quality and reproductive function by dietary supplementation with different types of antioxidants has been extensively evaluated, and thus a clear association between antioxidant consumption and improvements in sperm quality has been successfully documented [8-10].

TetraSOD® is a natural and healthy ingredient derived from the green marine microalgae species *Tetraselmis chuii*. It is produced under patent-protected technology by the company Fitoplancton Marino, SL (El Puerto de Santa María, Cádiz, Spain), exhibiting a high Superoxide dismutase (SOD) activity [11]. Moreover, TetraSOD® displays a balanced nutritional composition in terms of proteins, lipids, and carbohydrates, and also contains vitamins, minerals, essential fatty acids, pigments, amino acids, and polyphenols, all of them being potentially bioactive [11]. In previous studies, TetraSOD® has been demonstrated to act as a potent indirect antioxidant both *in vitro* and *in vivo*. In human skeletal muscle myoblasts, TetraSOD® stimulated the activity of the main cellular antioxidant enzymes: SOD, Glutathione peroxidase (GPx), and Catalase (CAT), and this effect occurred in parallel to the up regulation of genes encoding such enzymes [12]. Moreover, two key antioxidant genes, NRF2 and HMOXI, were also up regulated. The transcriptional activation of SOD, GPx, and CAT was probably a consequence of the first up-regulation of the transcription factor NRF2, which is known to activate not only primary protective antioxidant enzymes but also inducible phase II detoxifying enzymes such as HMOX1 [13,14]. In an animal model (rats), TetraSOD® was able to increase SOD, GPx, and CAT activities in muscle [15], and in the liver, it induced an increase in glutathione content together with up-regulation of genes involved in glutathione biosynthesis and recycling, as well as those encoding the primary antioxidant enzymes [16]. These basic effects might be related to the observed improvements in physical performance and recovery of sports people after consumption of 25 mg of TetraSOD® for variable time spans [15,17-19].

Therefore, given the demonstrated capacity of TetraSOD® to induce cellular antioxidant mechanisms, the aim of the present work was to assess the potential effects of the ingredient in the improvement of semen quality in idiopathic infertile men. With this purpose, a pilot trial was designed in which subjects were split into two different groups, each one supplemented with a different TetraSOD® dose (25 mg or 250 mg per day) for 90 days, thus covering a complete spermatogenesis cycle [20]. The main results are shown hereinafter.

Materials and Methods

Patients

This randomized single-blind pilot study was performed on a total of 40 individuals ranging from 18-45 years old. The participants were classified as infertile according to the criteria previously mentioned. Semen samples were initially obtained (t=0) and then analyzed according to the guidelines provided by the WHO [21]. The following parameters were determined: ejaculate volume, sperm concentration and total number, progressive motility, and normal forms. Participants could be thus diagnosed as suffering oligozoospermia, asthenozoospermia, or teratozoospermia (and/or their combinations) according to the Lower Reference Limits (LRL) established by the WHO [21] for each parameter (semen volume: 1.5 ml; total sperm number: 39 x 10^6 sperm per ejaculate; sperm concentration: 10^6 per ml; progressive motility: 32%; normal forms: 4%). Subjects were then randomly divided into two groups of 20 individuals each, receiving either 25 mg/day or 250 mg/day of TetraSOD® in a single capsule for 90 days. After the supplementation period (t=3 months), semen samples were collected again and analyzed as mentioned above, with the same parameters being determined.

Statistical Analysis

For each of the evaluated parameters, the differences between the two treated groups at each time point were determined using the Mann-Whitney test for unpaired data. The differences between before (t=0) and after treatment (t=3 months) were assessed for each experimental group using the Wilcoxon signed rank test for paired samples. In all instances, statistical significance was accepted for $p<0.05$.

Results

For each parameter, the obtained results are presented in Figure 1. At t=0, no statistically significant differences were observed for any parameter between individuals targeted to either 25 mg/day or 250 mg/day group, indicating initial homogeneity of the two experimental groups. However, after the supplementation period with TetraSOD®, individuals consuming 250 mg/day exhibited significantly higher values than those receiving 25 mg/day in semen volume (3.09 ml vs 2.45 ml), sperm concentration (17.16 vs 11.63 x 10^6 sperm/ml), total sperm number (52.75 vs 28.17 x 10^6 sperm), and progressive motility (32.85 vs 26.10%). Moreover, the 90 days supplementation period with 250 mg/day provoked significant increases in relation to initial values at t=0 in semen volume (34.93%), sperm concentration (86.16%), total sperm number (137.6%), and progressive motility (25.86%). Additionally, supplementation with 250 mg/day allowed

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sperm concentration, total sperm number, and progressive motility to be over the respective LRL established by the WHO [21]. The group receiving 25 mg/day also exhibited significant increases (although lower compared with 250 mg/day) at t=3 months when compared to t=0 in semen volume (21.29%) and total sperm number (77.74%), but not in sperm concentration and progressive motility. Finally, no significant effect of TetraSOD® supplementation was observed in normal forms.

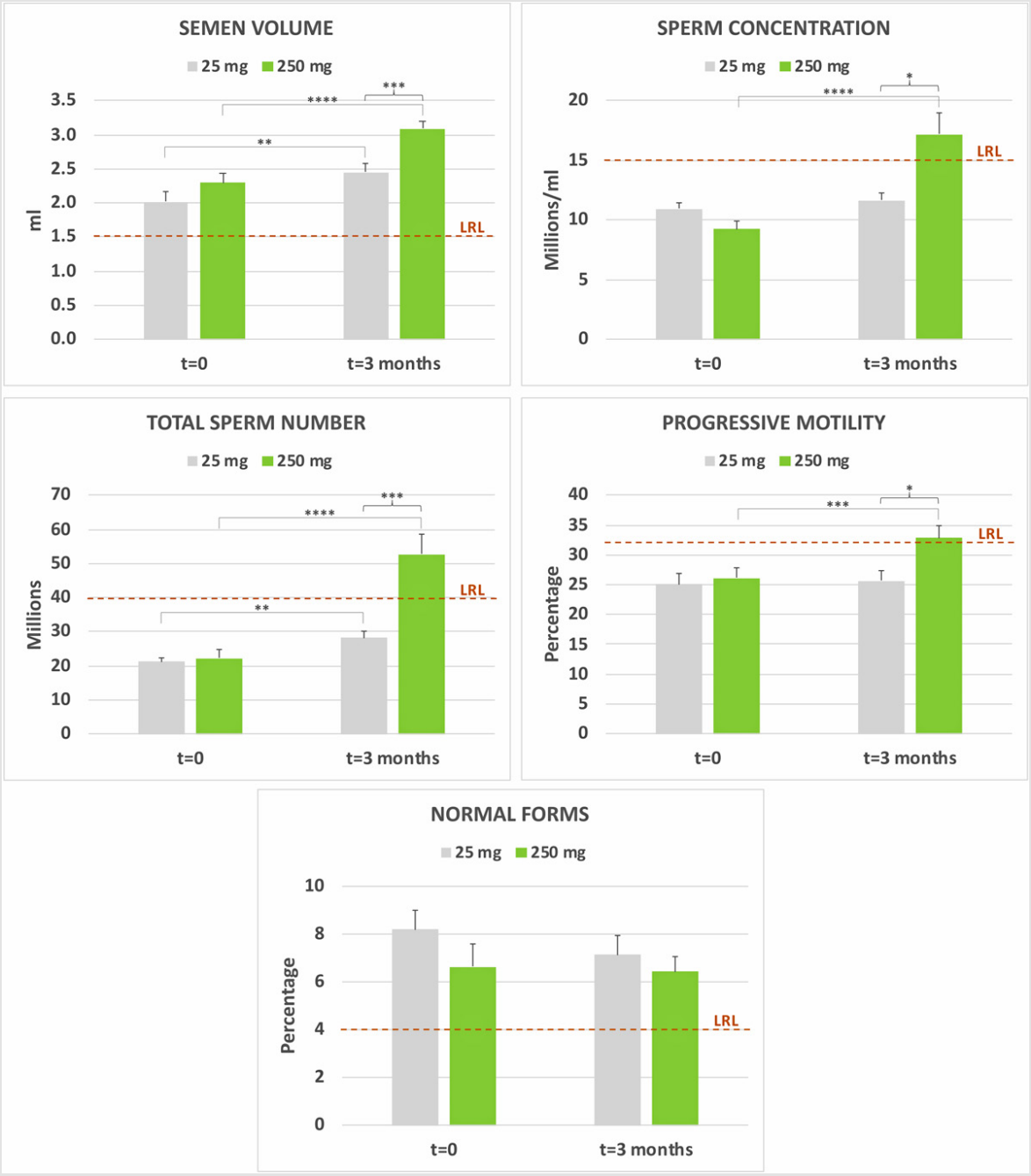

Figure 1: Observed values for the different seminal parameters at the commencement of the trial (t=0) and after the 90 days supplementation period (t=3 months) with either 25 mg or 250 mg per day of TetraSOD®. The LRL for each parameter (see Materials and Methods) is represented by a dashed line. Statistically significant differences are represented by asterisks (* p<0.05; ** p<0.01; *** p<0.001; **** p<0.0001).

Discussion

Microalgae are a natural source of bioactive compounds with potential applications for the treatment of infertility, as most of them exhibit antioxidant properties [22]. In this scenario, some species such as Chlorella or *Spirulina* have been extensively studied in animal models of induced infertility, in most instances being able to restore sperm parameters like basal levels [23]. The effects on boar fertility of dietary supplementation with the microalgae *Schizochytrium* enriched in the omega-3 docosahexaenoic acid have also been assessed, increasing semen volume and total sperm number [24]. Particularly in humans, *Spirulina* supplementation has been already evaluated in idiopathic infertile men, showing potential beneficial effects in sperm motility and morphology [25]. The results of this pilot study provide initial evidence that TetraSOD® supplementation (250 mg/day for 90 days) may improve semen quality in men with diagnosed idiopathic infertility. However, the present study has two main limitations. First, it was designed in the absence of a placebo experimental group. Although, the observed dose-dependent effects of TetraSOD® strongly suggest a negligible placebo effect. Second, a limited number of patients was included in the trial, as it was carried out as a prospective study. Therefore, the results presented here might be validated in a further double-blind randomized placebo-controlled trial including a higher number of individuals. Moreover, the inclusion of intermediate doses between 25 mg/day and 250 mg/day of TetraSOD® would help to better define the range of doses with clinically relevant effects.

Conclusion

A 90-day dietary supplementation period with 250 mg/day of TetraSOD® increased semen volume, sperm concentration, total sperm number, and progressive motility in idiopathic infertile men. These results suggest that TetraSOD® may enhance male fertility.

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Conflict of Interest

EC, CU, LM, and CI are employees of Fitoplancton Marino, SL.

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