



# Moderate aerobic exercise training for improving reproductive function in infertile patients: A randomized controlled trial



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## ABSTRACT

This study investigated for the first time the changes in seminal markers of inflammation, oxidative stress status, semen parameters, sperm DNA integrity as well as pregnancy rate following 24 weeks of moderate aerobic exercise in infertile patients. A total of 1026 sedentary men (aged 25–40 years) attending the infertility clinic with history of more than one year of infertility, were screened and 419 were randomized to either exercise (EX,  $n = 210$ ) or non-exercise (NON-EX,  $n = 209$ ) groups. Exercise training favorably attenuated seminal markers of both inflammation (IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ ) and oxidative stress (ROS, MDA, 8-Isoprostane) as well as enhanced antioxidant defense system (SOD, catalase and TAC) ( $P < 0.05$ ). These changes correlate with favorable improvements in semen parameters, sperm DNA integrity and pregnancy rate ( $P < 0.05$ ). The results provide information about the effectiveness of moderate aerobic exercise training as a treatment option for male factor infertility. The 4-week detraining period was not enough to reverse all benefits promoted by exercise intervention.

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## 1. Introduction

Infertility is characterized by the inability of a couple to achieve a clinical pregnancy within one year or more of regular, unprotected and well-timed intercourse [1]. It is a worldwide problem and affects 15% of all couples of reproductive age, with about 50% being associated with impairments in the process of spermatogenesis and sperm function, called male factor infertility [2]. In fact, spermatogenesis and sperm function can be compromised owing to a number of factors such as high level of reactive oxygen species (ROS) and oxidative stress [3]. ROS-induced oxidative stress has already been correlated with negative changes in semen parameters [4] and DNA fragmentation [5], leading to poor semen quality and is the cause of infertility in men [3]. A number of authors further showed oxidative stress in the seminal plasma can be related to inflammatory conditions therein [6]; and men with an excessive production of ROS by sperm demonstrated to have elevated levels of proinflammatory cytokines and leukocytes infiltration in their semen [7]. Positive correlations also were demonstrated between proinflammatory cytokines IL-6 or IL-8 with lipid peroxidation as well as sperm DNA fragmentation [8]

in male genital tract inflammation. Proinflammatory cytokines in seminal plasma furthermore have been reported to negatively influence standard semen quality parameters [9,10], as well as were found to damage sperm membranes and induce a significant loss of genomic integrity [11], all of which may have serious consequences for spermatogenesis and eventually male fertility.

Data from recent studies consistently show an association between physical activity and male reproduction [12–18]. For instance, a more recent randomized controlled trial conducted by our research laboratory [19] found that, in healthy human subjects, moderate intensity aerobic exercise training can induce significant improvements in semen parameters and sperm DNA integrity mainly through adaptations in the seminal antioxidant defense system and attenuating seminal markers of inflammation. To date; however, there are no published reports on the effects of exercise training on reproductive function in men with impaired fertility. Therefore, taking into account the role of markers of inflammation and oxidative stress in male reproductive function and potential effects of exercise training on seminal inflammatory mediators and redox homeostasis, we hypothesized that, in infertile men, the moderate aerobic exercise training, as a novel treatment option, would be successful in reducing chronic inflammation and oxidative stress in seminal plasma and those changes would be correlated to improvements in spermatogenesis and eventually male reproductive function. This randomized controlled trial, thus,

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was conducted to evaluate the effects of 24 weeks of moderate aerobic exercise training on markers of male reproduction including seminal markers of oxidative stress and inflammation, semen quality parameters, sperm DNA integrity and pregnancy rate in infertile patients. To the best of our knowledge, ours is the first study to address this issue.

## 2. Materials and methods

### 2.1. Experimental design and patients

A total of 1026 sedentary men (aged 25–40 years) attending the infertility clinic with a history of infertility longer than 12 months, were considered for inclusion in the study. All the patients had a history of infertility with no indication of hormonal, infective or physical causes. To be qualified to take part in the study, they had to be married men 25–40 years of age; not participating in a regular exercise program or accumulating 25 min or more of moderate physical exercise on 3 or more days a week; in good health, as ascertained through a routine physical examination and laboratory tests over the past 12 months; with no history of chronic illnesses, serious systemic diseases, testicular varicocele, genital infection and leukocytospermia; with no history of use of antioxidants as supplements like vitamins and medications known to alter the hypothalamic-pituitary-gonadal (HPG) axis, like anabolic steroids; with no history of cigarette use and alcohol consumption over the past 6 months; with no history of depression and eating disorders; with normal physical development and sexual maturation; not involving in occupations where the activity might influence fertilizing capacity; and had not undergone vasectomy reversal or varicocele removal surgeries. To be included in the study, patients had to be able to increase their level of physical activity as well. All patients were also needed to have stopped all medical therapy  $\geq 12$  weeks before study initiation [12,13,15,16,19].

Each patient provided 3 semen samples at 3-week intervals. All semen samples were evaluated in same laboratory and, on the basis of the fifth edition of World Health Organization (WHO) laboratory manual for the examination and processing of human semen [20], were classified into groups of asthenozoospermic (progressive sperm motility  $<32\%$  motile), asthenoteratozoospermic (progressive sperm motility  $<32\%$  motile, sperm morphology  $<4\%$  normal), oligoasthenozoospermic (sperm concentration  $<15 \times 10^6$  sperm/mL, progressive sperm motility  $<32\%$  motile), oligospermic (sperm concentration  $<15 \times 10^6$  sperm/mL), and oligoasthenoteratozoospermic (sperm concentration  $<15 \times 10^6$  sperm/mL, progressive sperm motility  $<32\%$  motile, sperm morphology  $<4\%$  normal) to give a total of five infertile subgroups. Patients were excluded for having azoospermia, leukocytospermia (leukocyte concentration  $>10^6$ /ml of ejaculate) and semen hyper-viscosity. Each patient was evaluated by a full review of their clinical history, physical examination and routine biochemistry analysis, with any clinically significant abnormalities in any of these tests leading to exclusion from the study. A certificate attesting to the patient's ability to participate in the study protocol was provided by the physician, and served as the final screen for participation in the study.

Once they met the inclusion criteria, eligible patients (asthenozoospermic,  $n = 83$ ; asthenoteratozoospermic,  $n = 84$ ; oligoasthenozoospermic,  $n = 80$ ; oligospermic,  $n = 88$ ; and oligoasthenoteratozoospermic,  $n = 84$ ) were further randomized to either exercise (EX) or non-exercise (NON-EX) groups, then provided written informed consent and entered the study (Table 1). With an  $\alpha = 0.05$ , an effect size = 0.95 and a power of 0.94, a sample size of 40 was recommended. Randomization using random number generation was used to assign patients to intervention groups.

This randomized controlled trial conducted in Dr. Bakhtyar Tartibian's Exercise Physiology Laboratory of the Urmia University (Iran) from March 2014 to September 2014. The data analyses were also conducted in Urmia University of Iran. The research protocol was approved by the Human Subject Internal Review Board Committee of the Urmia University (Iran). Thirty-three patients (asthenozoospermic,  $n = 8$ ; asthenoteratozoospermic,  $n = 8$ ; oligoasthenozoospermic,  $n = 4$ ; oligospermic,  $n = 11$ ; and oligoasthenoteratozoospermic,  $n = 2$ ) could not complete the study protocol, the remaining 386 patients are included in the analysis (Fig. 1).

### 2.2. Exercise protocol

Baseline testing included a maximal oxygen uptake ( $VO_{2max}$ ) with the use of an automated breath-by-breath system (CPX, Medical Graphics, St. Paul, MN, USA). Exercise sessions began between 5 and 7 pm. Moderate aerobic exercise protocol included walking or jogging on a treadmill supervised through certified personal trainers. During the first 12 weeks of the study, the EX groups exercised (25–30 min/day, 3–4 days/week) at 45–55% of their  $VO_{2max}$  and then the volume and the intensity of exercise sessions were increased during the final 12 weeks (40–45 min/day, 4–6 days/week, and 56–69% of  $VO_{2max}$ ). Adherence to the exercise was acknowledged via Polar heart rate monitors, and patients received immediate feedback to adjust to the prescribed intensity [19,21,22]. Patients with training adherence less than 95% were excluded. The NON-EX group patients were requested to maintain their current physical activities and not to modify their lifestyles during the 24-week intervention period.

### 2.3. Dietary and medication intake measures

Trained dietitians collected dietary data at baseline and 30 days post training using a validated semi-quantitative food frequency questionnaire (FFQ) [12,13,15–17,19]. Patients were asked to maintain their normal diet during the study period and were encouraged to eat a similar diet as far as possible in each sampling days. Patients were required to avoid any prescriptive or over the counter medications/supplements and foods that may impact the reproductive function one week before and during the study. Standard and self-reported questionnaires were also used to obtain information on use of medications/supplements during the study period.

### 2.4. Sampling

Patients reported to the lab on sampling days after complete sexual abstinence of at least 3–4 days. Patients were given clear instructions about the procedure of semen collection by masturbation into a sterile wide-mouth and metal-free plastic container at site. The initial semen sample was drawn 24 h before training session (baseline). Additional samples were collected 24 h after the last training sessions in weeks 12 and 24; as well as 7 and 30 days during recovery. Patients were asked not to exercise during the recovery period.

### 2.5. Analysis and measurements

Semen analysis was performed, following liquefaction (at least 30 min), to assess semen volume, sperm motility, sperm morphology, sperm concentration, and number of spermatozoa according to WHO guidelines for the examination of human semen [20]. The supernatant seminal plasma was frozen after a 10 min centrifugation (10,000g) at  $-80^\circ\text{C}$  until examination [23]. The same experienced technician performed semen evaluations during the study for the assessment of percentage of TUNEL positive sperma-

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