IJMS
Vol 51, No 1, January 2026

Original Article

# Probiotics Outperform Antioxidants in Improving Semen Parameters of Men with Idiopathic Oligoasthenoteratozoospermia: A Randomized Controlled Trial

Farshad Gholipour[1], MD; Davoud Gharakhani[2], MD; Amirhossein Rahavian[3], MD; Mahdi Norouzi[4], MD; Mohammadreza Hajian[5], MD; Serajoddin Vahidi[2], MD; Mohammad Javad Nazarpour[1], MD; Farbod Khorrami[6], BSc

[1]Isfahan Kidney Disease Research Center, Isfahan University of Medical Sciences, Isfahan, Iran;
[2]Department of Surgery, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran;
[3]Andrology Research Center, Yazd Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran;
[4]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran;
[5]Nikan Research Institute, Isfahan, Iran;
[6]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

**Correspondence:**
Amirhossein Rahavian, MD;
Andrology Research Center, Yazd Reproductive Sciences Institute, Safaeih, BouAli ‹Postal code: 89168-77391, Yazd, Iran
**Tel:** +98 35 38247086
**Email:** amirrahavian1369@gmail.com
Received: 24 December 2024
Revised: 23 May 2025
Accepted: 20 June 2025

## What's Known

- Idiopathic oligoasthenoteratozoospermia treatment, as a leading cause of male infertility, poses various challenges. Current treatment hinges on conventional treatments, especially antioxidants.
- Probiotics are an accidentally found treatment for oligoasthenoteratozoospermia. This study, which stands as the first one, is an endeavor to indicate the application of probiotics and compare their therapeutic effects with antioxidants.

## What's New

- Probiotic and antioxidant, compared to baseline, exerted significant improvement in sperm concentration, motility, and morphology.
- Probiotics significantly outperformed placebo in sperm concentration, motility, and morphology. Additionally, probiotics indicated superiority to antioxidants in motility and morphology parameters.

## Abstract

**Background:** Idiopathic oligoasthenoteratozoospermia (iOAT) treatment still poses significant challenges. This study aims to compare the therapeutic efficacy of probiotics on sperm parameters of iOAT patients with placebo and antioxidants.
**Methods:** In this triple-blind, randomized controlled trial, 110 men with iOAT were assigned to receive either a probiotic (Familact®), an antioxidant (Sperigen®), or a placebo daily for 3 months, in two academic centers in Iran (Isfahan and Yazd). The study was conducted from July 2021 to April 2022. Sperm parameters were analyzed using computer-assisted semen analysis. The main measured outcomes included semen volume and sperm features, including motility, morphology, and concentration. Changes in semen parameters were assessed using linear mixed-effects models with fixed effects for time, group, and their interaction. Estimated marginal means were compared across groups using Bonferroni-adjusted pairwise tests.
**Results:** Overall, 110 men (mean age of 34.3±4.5 years) were included in the final analysis. Significant Time×Group interactions were found for sperm concentration ($P=0.003$), motility ($P<0.001$), and morphology ($P<0.001$), but not for semen volume ($P=0.71$). After 3 months, the probiotic group showed significantly greater improvements in sperm concentration ($10.42\pm1.11\times10^6$/mL, $P=0.007$), motility (46.65±3.73%, $P=0.001$), and morphology (4.31±0.21%, $P<0.001$) compared to the placebo group. Additionally, probiotics outperformed antioxidants in morphology ($P<0.001$) and motility ($P=0.009$).
**Conclusion:** This study is the first to directly compare probiotics and antioxidants in treating iOAT. Probiotics showed superior performance in sperm motility and morphology compared to antioxidants, although drawing a strong conclusion requires further robust studies.
**Trial Registration Number:** IRCT20150420021869N5.

Please cite this article as: Gholipour F, Gharakhani D, Rahavian AH, Norouzi M, Hajian MR, Vahidi S, Nazarpour MJ, Khorrami F. Probiotics Outperform Antioxidants in Improving Semen Parameters of Men with Idiopathic Oligoasthenoteratozoospermia: A Randomized Controlled Trial. Iran J Med Sci. 2026;51(1):39-46. doi: 10.30476/ijms.2025.105150.3888.

**Keywords** ● Probiotics ● Antioxidants ● Oligospermia ● Male infertility ● Andrology

## Introduction

Approximately 15% of all couples attempting to conceive experience infertility.[1] Infertility is defined as the inability to achieve pregnancy naturally after a year of regular and unprotected intercourse.[2] In about half of infertility cases, men are involved, while 20-30% of infertility cases are solely attributed to male factors.[3] Some identifiable causes of infertility include varicocele, cryptorchidism, and hypogonadism. However, in some cases, no apparent reasons for abnormal semen analysis lead to a diagnosis of idiopathic oligoasthenoteratozoospermia (iOAT).[1] iOAT, a diagnosis of exclusion, accounts for nearly 30% of male infertility cases, where sperm concentration and the proportion of motile and morphologically normal sperm are below the World Health Organization (WHO) standards.[1]

iOAT is typically treated empirically due to its multifactorial nature, making it difficult to pinpoint the exact cause through laboratory methods.[4] Several therapeutic approaches, including both hormonal and non-hormonal drugs, have been proposed to treat iOAT. One effective non-hormonal treatment option is the use of oral antioxidants.[5] Reactive oxygen species (ROS) play a significant role in male infertility, with higher levels found in infertile men. Therefore, antioxidants can be protective against the effects of ROS.[1]

In recent years, probiotics have gained recognition as a therapeutic option across diverse medical domains. Their limited adverse effects and wide-ranging impacts on different physiological systems make them an attractive choice for medical interventions.[6] Many studies suggest that probiotics can improve women's fertility.[7] In 2017, Maretti and colleagues serendipitously found that iOAT patients who received probiotics for digestive issues showed improvements in their semen parameters.[4] Following this discovery, further research has confirmed the positive effects of probiotics on semen parameters.[8-10] Two prior Iranian studies indicated the positive advantages of probiotics in enhancing semen parameters. Abbasi and colleagues,[8] showed the effectiveness of the symbiotic regimen in sperm parameters, including concentration, motility, and morphology in infertile males compared to placebo. Another study by Asadi and colleagues,[11] also stated the superiority of probiotics over placebo in terms of sperm concentration and morphology in infertile men who underwent varicocelectomy. However, no study has compared the efficacy of probiotics versus antioxidants.

Hence, considering the promising findings of probiotics' effects, their affordability, and the lower risk of complications, this randomized clinical trial (RCT) aims to compare the effects of probiotics and antioxidants on iOAT patients' sperm parameters.

## Materials and Methods

### *Study Population*

Male patients who visited the Yazd Infertility Center (Yazd, Iran) and Isfahan Urology Clinic (Isfahan, Iran) with primary idiopathic infertility were screened for eligibility. Men under the age of 45 who met the 2010 WHO infertility criteria, including having sperm parameters below the 5th percentile (sperm count <15,000,000/mL, normal morphology <4%, and motility A+B+C <40%), were included in the study.[12] The following individuals were excluded from the study: those with pyospermia, varicocele, a history of testis surgery or varicocelectomy, undergoing chemotherapy or radiotherapy, smokers, those with a history or current use of drugs that affect spermatogenesis such as tamoxifen, human Chorionic Gonadotropin (hCG), cytotoxic drugs, immunosuppressants, anticonvulsants, or androgens, those with a history of sexually transmitted diseases, epididymo-orchitis, testis trauma and/or torsion, prostatitis, chromosomal abnormalities, and those who declined to participate in the study.

### *Study Design*

This is a three-month-long, multi-center, triple-blinded, randomized, placebo-controlled clinical trial that was conducted from July 2021 to April 2022. A total of 203 male patients with infertility who were referred to both centers, 136 and 67 from Isfahan and Yazd centers, respectively, were evaluated for eligibility. Patients were evaluated by an experienced urologist specializing in infertility. They were interviewed to gather demographic information, ascertain the duration of infertility, and obtain a history of any illnesses or medication usage. Following the completion of the patient history, a testis examination was conducted. Subsequently, the patients were randomly divided into three parallel groups using the Random Allocation Software.[13] All patients who were referred to both centers and satisfied the primary criteria were further evaluated for inclusion. After obtaining informed consent, the patient would be randomly and uniformly assigned to each of three groups at the first visit, and would stay blind to the process through the study. Simple randomization was used to allocate participants into three parallel groups (probiotic, antioxidant, and placebo) in a 1:1:1 ratio. This was conducted using Random Allocation Software, which assigned each participant a random code to ensure allocation concealment. Each new patient at the time of enrollment was assigned to the next available random code, which corresponded to a concealed group assignment. Subsequently, the participant, care provider, and analyzer were blinded. A per-protocol approach was considered to ensure the robustness of analyzing the results in the *post hoc* analysis.

Both centers, which were tertiary academic hospitals, adhered to a shared protocol in study design, patient selection, and follow-up. The first group was administered a daily diet of two capsules of probiotic Familact® (Zist Takhmir, Iran), the second group received two capsules of mineral multivitamin Sperigen® (Hayat Darou, Iran), and the third group received two capsules of the placebo, which was also produced by Zist Takhmir Company. The placebo and the probiotic were indistinguishable in appearance but slightly different from the antioxidant. All medications were in capsule form. Each patient took a capsule every 12 hours for 90 days.

Familact® is a synbiotic that contains a variety of beneficial strains, including *Lactobacillus casei, Lactobacillus rhamnosus, Lactobacillus acidophilus, Lactobacillus bulgaricus, Streptococcus thermophilus, Bifidobacterium longum,* and *Bifidobacterium breve.* Additionally, it includes fructooligosaccharides as prebiotics.[8]

Sperigen® comprises a combination of group B vitamins, vitamin A, vitamin C, vitamin E, selenium, zinc, glutathione, L-carnitine, L-arginine, CoQ10, and other supplements.

### *Sample Collection and Semen Analysis*

Four semen samples were collected from each patient. Two samples were obtained before the intervention, and two samples were collected three months after the intervention. In both instances, the samples were taken one week apart following 48 hours of ejaculatory abstinence. The semen samples were collected via masturbation in a private room at the laboratory and analyzed using the Computer-Assisted Sperm Analysis (CASA, Video Test, Version Sperm 2.1©, Russia) method within 30 min. The average value of the two samples was calculated both before and after the intervention.

The main outcome of the study was post-intervention semen parameters. Sperm concentration was measured using a sperm counting chamber (Shivani Scientific Industries, Mumbai, India). Sperm motility and morphology were assessed using a computerized sperm analysis system called Video Test (CASA, Video Test, Ltd: version Sperm 2.1, Russia). The interpretation of semen parameters was conducted according to the WHO 2010 criteria.[12] Both centers utilized the same sample-gathering and analyzing procedures.

### *Ethical Considerations*

This RCT adhered to the principles outlined in the 1964 Helsinki Declaration and its further updates. The study was conducted from July 2021 to April 2022, following approval by the local research ethics committee, under the ethical code of IR.MUI.MED.REC.1400.443. Informed consent was obtained from all participants before their involvement in the study. The RCT has been registered on the Iranian Registry of Clinical Trials under the code IRCT20150420021869N5.

### *Statistical Analysis*

Statistical analyses were conducted using SPSS® version 26.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±standard deviation. The normality of the data was assessed using the Kolmogorov-Smirnov test. All four key semen parameters (volume, concentration, motility, morphology) were analyzed using linear mixedeffects models with restricted maximum likelihood estimation (REML) and an unstructured covariance matrix for the repeated measures. In each model, time (baseline vs. 3 months), group (antioxidant/probiotic vs. probiotic vs. placebo), and their interaction (Time×Group) were included as fixed effects, and patient ID was included as a random intercept. We also adjusted for the center as a fixed effect. Estimated marginal means (EMMs) and their standard errors (SEs) at each time point and group were obtained, and pairwise comparisons at 3 months were Bonferroniadjusted. The primary hypothesis test was the Type III Ftest of the Time×Group interaction; P<0.05 was considered statistically significant.

## Results

### *Baseline Characteristics*

Table 1 presents the basic characteristics of the patients included in the study. A total of 110 men with a mean age of 34.3±4.5 years were included in the final analysis. Sixty-three patients were recruited from Center 1, and 47 patients were recruited from Center 2. Among them, 38, 35, and 37 patients were assigned to the antioxidant, probiotic, and placebo groups, respectively (figure 1). In assessing treatment compliance, 94.9%, 97.2%, and 92.7% of patients in the placebo, probiotic, and antioxidant groups, respectively, adhered to their prescribed treatment regimen.

There were no significant differences observed between the study groups in terms of age and duration of infertility (P=0.158 and 0.326, respectively).

**Table 1:** Baseline characteristics (n=110)

| | Antioxidant (n=38) | Probiotic (n=35) | Placebo (n=37) | P value[a] |
|---|---|---|---|---|
| Age (years, median [Q1-Q3]) | 34 (29-38) | 35 (30-39) | 32 (28-36) | 0.158 |
| Infertility period (months, median [Q1-Q3]) | 31 (24-40) | 31 (25-38) | 32 (26-42) | 0.326 |

[a]Kruskal-Wallis H test, P<0.05 was considered significant.

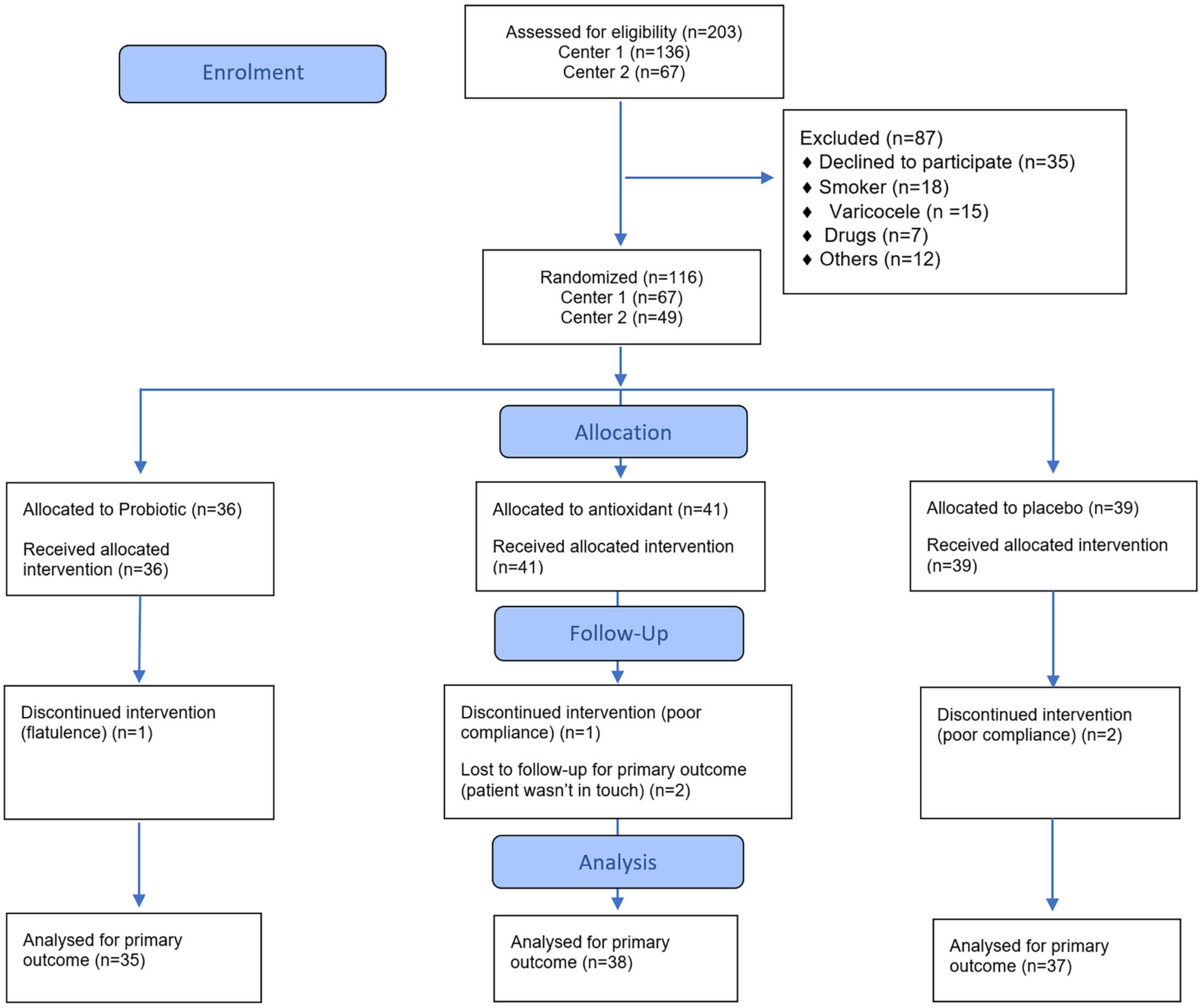


**Figure 1:** This figure outlines the flowchart of the study.

In the probiotic group, one patient discontinued the treatment due to flatulence. No other drug-related adverse events were reported by the patients.

*Sperm Concentration*

Table 2 represents the results of sperm parameters of the three groups at baseline and after 3 months. The mixed effects model showed a significant Time×Group interaction for concentration (F [2,107]=5.976, P=0.003), indicating that changes over time differed by treatment group. The probiotic group had significantly higher concentration than placebo (mean difference=5.51×10⁶/mL, P=0.007), whereas the difference between probiotic and antioxidant did not reach significance (P=0.89), nor did antioxidant vs. placebo (P=0.11).

*Sperm Motility*

A significant interaction was also observed for motility (F (2,106)=13.453, P<0.001). Pairwise tests at 3 months showed probiotic outperformed antioxidant (P=0.009) and placebo (P=0.001), with no difference between antioxidant and placebo (P>0.999).

*Sperm Morphology*

The Time×Group interaction was likewise highly significant (F[2,107]=29.254, P<0.001). At 3 months, the probiotic outperformed both antioxidant (P<0.001) and placebo (P <0.001); antioxidant vs. placebo was not significant (P=0.15).

**Table 2:** Adjusted marginal means of semen parameters at baseline and 3 months by treatment group, with Group×Time interaction tests and Bonferroni-adjusted pairwise comparisons

| Parameter | Baseline adj. mean±SE | 3-month adj. mean±SE | Group×Time P value[a] | Pairwise comparisons at 3 months[b] |
|---|---|---|---|---|
| Semen volume (mL) | 3.62±0.23[c] | 4.09±0.35 | 0.710 | >0.999[#] |
| | 3.67±0.2[d] | 4.11±0.36 | | >0.999[^] |
| | 3.49±0.23[e] | 3.60±0.35 | | >0.999[$] |
| Sperm concentration ($\times 10^6$/mL) | 5.03±0.50[c] | 8.55±1.07 | 0.003 | 0.89[#] |
| | 5.13±0.52[d] | 10.42±1.11 | | 0.11[^] |
| | 4.79±0.51[e] | 4.91±1.08 | | 0.007[$] |
| Sperm motility (%) | 22.16±2.00[c] | 26.58±3.58 | <0.001 | 0.009[#] |
| | 23.54±2.08[d] | 46.65±3.73 | | >0.999[^] |
| | 21.72±2.02[e] | 22.75±3.67 | | 0.001[$] |
| Sperm morphology (%) | 1.47±0.15[c] | 2.21±0.20 | <0.001 | <0.001[#] |
| | 1.60±0.15[d] | 4.31±0.21 | | 0.15[^] |
| | 1.47±0.15[e] | 1.52±0.20 | | <0.001[$] |

[a]P<0.05 was considered significant; [b]Bonferroni test; [c]Antioxidant; [d]Probiotic; [e]Placebo; [#]Antioxidant vs Probiotics; [^]Antioxidant vs. Placebo; [$]Probiotic vs. Placebo

*Semen Volume*

The interaction for volume was not significant (F(2,107)=0.339, P=0.71), with no pairwise differences (all P>0.999).

## Discussion

This study is the first to directly compare the effects of probiotics and antioxidants on semen parameters. The findings suggest that probiotics, despite being less costly, exhibit superior functionality in enhancing sperm features in patients with iOAT.

A plausible hypothesis regarding the etiology of iOAT is the mild alterations in the pulsatile secretion of gonadotropins and testosterone.[14] It appears that probiotics can regulate gonadotropin secretion and enhance fertility through their interaction with kisspeptin.[15] Another hypothesis regarding the etiology of iOAT is the elevation of oxygen-free radicals in the seminal fluid. Probiotics can potentially treat iOAT by reducing the levels of oxygen-free radicals.[16, 17] Additionally, changes in the prostatic microenvironment are another hypothesis underlying iOAT, which can be improved by probiotics.[18] One rationale for the superior effectiveness of probiotics over antioxidants in enhancing sperm motility and morphology is their multifaceted mechanisms of action beyond their antioxidant effects.

In our study, only the probiotics group showed improvement in sperm concentration compared to the placebo. Although previous studies on antioxidants have reported increases in sperm concentration ranging from 23% to 78%, which aligns with our findings of a 70% improvement.[1, 3, 19, 20] Regarding probiotics, a few studies have demonstrated increases in sperm concentration ranging from 28% to 86% with probiotic consumption.[4, 8, 9] In our study, probiotics significantly improved sperm concentration by 103%, which was more effective than antioxidants. However, a study by Valcarce and colleagues showed improvement only in sperm motility and DNA fragmentation index (DFI), which could be attributed to the smaller sample size (nine individuals) and shorter duration of probiotic consumption (6 weeks) than other studies.[10] Asadi and colleagues' study,[11] on probiotics consumption after varicocelectomy, resulted in significant improvement in sperm concentration and morphologically normal sperm compared to placebo controls. These findings align with the results of our study.

According to our findings, both probiotics and the antioxidants group exhibited improvements in sperm motility, which is in line with previous literature on antioxidants[1, 3, 19, 20] and probiotics.[4, 8, 9] In our study, the antioxidants group showed a 20% improvement in sperm motility, which falls within the range reported by other studies (12% to 31%).[20-24] However, Nazari's study did not observe any improvement in sperm motility following antioxidant intake.[25] In the limited studies conducted on probiotics, the improvement in sperm motility ranged from 31% to 159%.[4, 8, 9] Our rate was 98%. The probiotics significantly outperformed antioxidants regarding this feature. It appears that sperm motility responds more favorably and quickly to probiotics, as evidenced by improvements observed in all studies conducted on probiotics.

Here, the antioxidant group showed a 50% increase in sperm with normal morphology, while the probiotic group demonstrated a substantial 170% increase. These rates align with previous studies reporting increases ranging from 25% to 86% for antioxidants,[20, 22, 25] and 52% to 132% for probiotics.[4, 8] However, studies by Alahmar and Szymański did not observe improvements in the rate of sperm with normal morphology following antioxidant consumption.[21, 26] Similarly, Valcarce and Helli's studies did not find any improvement in morphology with probiotic intake.[9, 10] It is worth noting that the duration of probiotic consumption in Valcarce's and Helli and colleagues' studies was 6 and 10 weeks, respectively. It can be inferred that the lack of morphological improvement in these two studies may be attributed to the relatively shorter duration of supplement usage.

We did not observe any significant changes in seminal fluid volume following the consumption of antioxidants or probiotics, which is consistent with previous studies on antioxidants[1, 3, 19, 20] and probiotics.[8, 10] However, in some studies, probiotics have been found to increase seminal fluid volume.[4, 9] It appears that probiotics have a lesser effect on semen parameters when used for a shorter duration. For instance, in a study by Valcarce and colleagues,[10] patients consumed probiotics for 6 weeks; only improvements in sperm motility and DFI were observed compared to the control group. Conversely, in Maretti and colleagues' study,[4] where probiotics were consumed for 6 months, improvements were seen not only in other semen parameters but also in seminal fluid volume.

Maretti and colleagues[4] also reported that probiotics could increase testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) levels. Additionally, in an animal study, probiotics were found to increase testosterone levels and testicular size.[27] In Helli and colleagues' study,[9] probiotics led to an increase in testosterone levels, although it was not statistically significant. Furthermore, it has been documented that the use of probiotics can reduce inflammatory responses and oxidative stress.[9, 28] Therefore, it can be postulated that probiotics may treat iOAT by increasing testosterone levels, mitigating inflammatory responses, and reducing free radicals and oxidative stress. Probiotics exert their effects through multiple mechanisms, whereas antioxidants primarily act by reducing oxidative stress. Thus, it is not surprising that probiotics outperformed antioxidants in improving semen parameters.

Our study had several limitations. Firstly, we solely examined the effect of probiotics on semen analysis and did not assess other outcomes, such as hormonal profiles, DFI, or the antioxidant capacity of semen, given the multifactorial effects of probiotics, which are crucial factors that must be considered by future studies. Secondly, our study was of short duration, and we did not have the opportunity to assess fertility rates or the success of assisted reproductive methods during this time. We did not have information regarding the duration of the effects of probiotics after they were discontinued. Fourthly, we did not evaluate the impact of combining antioxidants with probiotics on semen parameters. Fifthly, while different brands of included treatments share similar ingredients, utilizing standard, affordable, and available medications through both centers poses a challenge. Lastly, the results of our study may have limited applicability to all the antioxidant and probiotic products available on the market due to the wide variety. Therefore, we suggest RCTs with longer follow-up periods, focusing on determining the best dosing and combination of antioxidants with probiotics, identifying the most effective probiotic strains, and assessing additional outcomes, including fertility rates, DFI, and hormonal profile, in future studies.

## Conclusion

In conclusion, a 12-week intake of probiotics in men with iOAT led to improvements in sperm concentration, motility, and normal morphology. Probiotics exhibited superior effectiveness compared to antioxidants in enhancing semen parameters.

## Authors' Contribution

F.GH contributed to conceptualization, methodology, study design, investigation, data preparation, analysis, and manuscript writing and editing; A.R contributed to methodology, investigation, data preparation, and manuscript writing and editing; D.GH contributed to the data preparation, investigation, and manuscript writing and editing; M.H and S.V contributed to data gathering, investigation and writing; MJ.N contributed to methodology, investigation, and manuscript editing; M.N contributed to the investigation, analysis, manuscript writing and editing; F.K contributed to the investigation and manuscript writing and editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Declaration of AI

The authors declare that QuillBot AI was used solely to improve the clarity of language, grammar, and writing style of the manuscript. No AI tool was used for data analysis, interpretation of results, or generation of scientific content.

**Conflict of Interest:** None declared.

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