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Resistance Exercise With Herbal Supplements Improving the Sperm Status of Infertile Men

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ABSTRACT

Background: Infertile men have higher levels of sperm reactive oxygen species (ROS) compared to fertile men. The high level of free radicals in semen can disrupt sperm function, damage sperm DNA, and reduce male fertility. We investigated the effect of resistance exercise alone or together with ginger and date palm pollen (DPP) supplements, as well as these two supplements alone, on sperm quality in infertile men with oligoasthenotratospermia (OAT).

Materials and Methods: This randomized, single-blinded trial was conducted on 48 infertile men with OAT. The volunteers were randomly assigned to 6 groups: Exercise (8 people), DPP (8 people), ginger (8 people), DPP+exercise (8 people), ginger+exercise (8 people) and control (placebo) (n=8). Participants in the ginger and ginger+exercise groups were taken two capsules (250 mg ginger) and also in DPP and DPP+exercise, two capsules (DPP 250 mg) daily for two months. Before and after the treatment, semen and blood samples of the participants were collected. Also, the semen was analyzed according to World Health Organization (WHO) reference value. DNA fragmentation and hormonal profile (luteinizing hormone [LH], follicle stimulating hormone [FSH] and testosterone) were determined by TUNEL and ELISA kit.

Results: The sperm motility increased significantly in the supplements alone and supplements with exercise groups compared to before the treatment (DPP: P=0.006; ginger=0.04; DPP+exercise: P=0.001; ginger+exercise: P=0.002). Sperm concentration had a significant increase in the supplement alone and supplements+exercise groups (DPP: P=0.013; ginger=0.005; DPP+exercise: P=0.001; ginger+exercise: P=0.01), while no significant difference was observed in the normal morphology of sperm. The DNA fragmentation index level in all studied groups, except the control group, showed a significant decrease. Also, a significant increase in the levels of the studied hormones was observed in all groups except the control group (DPP: P=0.016; ginger=0.007; DPP+exercise: P=0.025; ginger+exercise: P=0.008 and exercise=0.006). FSH and total testosterone (TT) increased after consuming the DPP or ginger or doing exercise alone or along with supplements. While the increase of LH in all of groups was significant except exercise group and control.

Conclusion: Ginger, DPP and exercise have positive effects on the sperm quality of infertile men.

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Introduction

Physical inactivity may be associated with increasing infertility among families. Today, evidence shows that approximately 15% of all couples of childbearing age are infertile. Also, in more than half of infertile couples who undergo assisted reproductive techniques, disruption of spermatogenesis and sperm function mainly contribute to infertility, which is called male factor infertility [1]. Spermatogenesis can be affected by testicular thermal stress, oxidative stress, obesity, modern lifestyle, endocrine disease, unhealthy diet, side effects of drugs, and radiation. Today, due to the invasiveness of most male infertility treatment methods and their high costs, researchers look for easier and less expensive methods with fewer complications. Sport training is prescribed by physicians as an efficient and inexpensive method for diseases, particularly for the cardiovascular system [2].

Some studies demonstrate that the combination of a healthy diet and exercise in obese mice improves the core parameters of sperm, including motility, morphology, DNA fragmentation, and mitochondrial reactive oxygen species (ROS). It has been documented that sports protocols, depending on the method of exercise or intensity of physical activity, can have a positive or negative impact on the quality of semen. Some studies have shown that regular physical activity improves parameters of semen quality and sperm DNA integrity in both fertile and infertile populations through the increase in anti-inflammatory markers and reduction of free radicals [3]. Similarly, some research on moderate-intensity physical activity has revealed an improvement in antioxidant capacity, testosterone level, and male reproductive potential [4]. On the contrary, it has been observed that exercising with high intensity and duration increases the damage to testicular tissue and sperm parameters by causing disturbances in the process of spermatogenesis and fertility through dysregulating the level of sex hormones [5]. Some studies have shown that hormonal changes are influenced not only by the amount of training but also by the intensity of the training [6]. Previous research has shown that doing resistance exercises increases sex hormones such as testosterone (T), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), as well as improves sperm parameters [7].

Research on the effects of herbal medicines on sperm parameters has shown their effectiveness in improving fertility [8]. The ginger root (*Zingiber officinale* L., Family Zingiberaceae), commonly used as a spice, is also medically used for its immunomodulatory, anti-tumorigenic, anti-inflammatory, anti-apoptotic and antioxidant properties [9]. Also, the administration of ginger significantly improved the sperm parameters, total testosterone (TT), LH and FSH levels in plasma [4, 10, 11]. On the other hand, date palm pollen (DPP) is the male reproductive dust of palm flowers used as a dietary supplement in treating male infertility [12]. DPP contains compounds such as amino acids, fatty acids, flavonoids, saponins, and stroles [13]. It has also been reported to improve sperm parameters, including motility and viability, acrosome reaction, and lipid peroxidation [14, 15].

Since DPP and ginger are medicinal plants with positive effects on fertility, especially accompanied by exercise, they may have useful effects compared to current treatment methods. However, there are still many contradictions about the effect of exercise and physical activity on male fertility. So, the purpose of this study was to investigate the effect of resistance exercises and consuming ginger and DPP on sperm parameters, DNA integrity, and LH, FSH and TT hormones in infertile men with oligoasthenoteratozoospermia (OAT).

Materials and Methods

Study design

This study was a prospective randomized, single-blinded trial (based on the CONSORT guidelines) [16] conducted between July 2020 and February 2021. This clinical trial was conducted in the IVF unit of the Infertility Treatment Center of the Academic Center for Education, Culture, and Research (ACECR) (Qom, Iran).

Forty-eight infertile men with OAT (according to World Health Organization (WHO) criteria, men with low sperm count, low motility [<40%] and normal sperm morphology <4% are diagnosed as OAT) [17] and an average age of 25-40 years took part in this study. The participants were randomly divided into 6 groups: Resistance exercise (n=8), DPP supplement (n=8), ginger supplement (n=8), resistance exercise+DPP (n=8), resistance exercise+ginger (n=8), and control (placebo) (n=8). In this study, capsules containing flour were provided to patients in the control group.

Participants in the groups with resistance training practiced the designed protocol in a sports club under the supervision of a trainer. Patients in the treatment groups took ginger supplement twice daily, 250 mg capsules each time (Zintoma, Goldaru, Iran) and pollen powder 250 mg in gelatinous capsules twice daily (in the morn-

ing and one hour before exercise) for two months [15, 18]. Semen and blood samples of the participants were collected before and after the treatment.

The inclusion criteria included infertility with concentration and motility of sperm lower than normal set by the WHO in 2010 [17]. The exclusion criteria included pathological features such as leukocytospermia, varicocele, hormonal disorders, presence of cryptorchidism, vasectomy, liver disorders, smoking and alcohol consumption, Klinefelter syndrome, cancer and total sperm count less than 10×10^6.

Intervention and assessment

Age, duration of infertility, height (m), weight (kg) and body mass index (BMI, kg/m^2) of infertile men participating in the study before and after the intervention were recorded and compared. Variables such as sperm parameters, DNA fragmentation index (DFI) and hormonal parameters (LH, FSH and TT) were measured and compared before and after the intervention.

Semen analysis

After 3 to 4 days of sexual abstinence, sperm samples were obtained through masturbation in sterile containers. The samples were collected and liquefied for 20 minutes at room temperature. Semen parameters, including sperm concentration, progressive and non-progressive motility, normal morphology and viability, were evaluated according to the WHO guidelines for fresh sperm. Sperm motility was assessed using a computer-aided sperm analysis (CASA) system (LABOMED, SD-C313B, Germany). Motility of sperm was classified into progressive, non-progressive and immobile. Normal morphology was assessed through Papanicolaou stain and sperm concentration was assessed by sperm counting chamber (Rohm, India) and recorded as million/mL [17].

DNA fragmentation assessment

Fragmentation of DNA was assessed using the terminal deoxynucleotidyltransferase nick end labeling (TUNEL) assay in an in situ cell death detection kit (Roche, Mannheim, Germany). According to the manufacturer's instructions, briefly in this method, 200 spermatozoa were randomly selected and evaluated with an Olympus fluorescent microscope (BX51, Tokyo, Japan) with a magnification of 100. Sperm with a red head was considered as sperm with intact DNA and sperm with a green head as sperm with fragmented DNA [19].

Hormonal analysis

Blood samples were taken from each participant before and after the intervention and centrifuged at 3000 rpm for 10 minutes (Hettich, EBA20, UK). Serum samples were stored at -70 °C for future analysis. In all samples, serum levels of LH (mIU/mL, Cat.N.DE1289), FSH (mIU/mL, Cat.N.DE1288) and TT (ng/mL, Cat.N.DE1559) were measured by using ELISA method (Demeditec Diagnostics GmbH, Germany) for hormonal profiling [20].

Exercise protocol

The resistance training protocol was as follows. One week before the research began, the samples participated in a familiarization session. Next, they received an explanation of the safety measures related to weight training and the correct techniques for exercising. To familiarize themselves, the participants performed submaximal repetitions for each movement, and then measured the one-repetition maximum (1RM) for the movements under consideration. The training program consisted of 24 sessions, 3 sessions per week for 8 weeks [21].

Resistance training started at 60% 1RM and increased by 5% every two weeks, ending at 75% 1RM in the final week. The amount of training weight and 1RM were calculated based on the maximum repetition record with the Berzensky formula [22], (Equation 1):

1. 1RM=Amount of weight/[1.0287-(Repetitions to failure×0.287)]

The exercises in each session included chest press, deadlift, squat, lat pull-down, and barbell shoulder press. However, the control and supplementary groups did not have any activity during the research period [21] (Table 1).

Statistical analysis

The data were evaluated with SPSS software, version 16. The normal distribution of data was assessed by the Kolmogorov-Smirnov test. Data were compared by the paired t-test before and after the treatment. Mean differences were considered statistically significant at $P\leq0.05$. All data were presented as Mean±SEM.

Result

Clinical and demographic characteristics

The average age and duration of infertility of the participants were 34.6±4.17 and 2.4±0.2 years, respectively.

Table 1. Resistance training protocol with an intensity of 70% to 60% of maximum repetitions

Week (Intensity of Training)	Type of Movement	Sets and Repetition	Rest Between Repetitions (s)	Rest Between Sets (s)
1st and 2nd (1RM 60%)	Chest press	3(8×10) repetitions	30	120
3rd and 4th (1RM 65%)	Dead lift squat			
5th and 6th (1RM 70%)	Lat pull down			
7th and 8th (1RM 75%)	Barbell shoulder press			

The average height and age of men did not change significantly after the intervention (Table 2). Our data showed that BMI decreased significantly in the exercise training groups (Table 3).

Comparing seminal parameters before and after the intervention

Our results showed that the total motility in the supplemented groups and supplemented+exercise groups were significantly increased compared to before the intervention (DPP: 19.375±2.57% vs 35.62±4.47%; P=0.006, ginger: 25±3.89% vs 35.50±3.77%; P=0.04, DPP+exercise: 23.75±2.23% vs 35.13±2.20%; P=0.001, ginger+exercise: 23.12±2.97% vs 31.87±2.09%; P=0.002, exercise: 29.37±2.20% vs 33.12±2.66%; P=0.265 and control: 23.12±2.48% vs 23.75%±2.26%; P=0.59) (Figure 1). Progressive motility increased significantly in DPP and ginger groups after treatment (6.875±2.302% vs 16.875±4.323%; P=0.037 and 6.25±2.79% vs 13.75±2.4 7%; P=0.040, respectively). However, this increase was not significant in other groups (Figure 2). Sperm concentration significantly increased in the supplemented and supplemented with exercise groups (DPP: $14.375\times10^6\pm1.58$ vs $21.87\times10^6\pm3.44$; P=0.013, ginger: $12.62\times10^6\pm1.83$ vs $17.12\times10^6\pm1.85$; P=0.005, DPP+exercise: $13.25\times10^6\pm1.73$ vs $22.87\times10^6\pm1.99$; P=0.00, ginger+exercise: $15.5\times10^6\pm1.30$ vs $19.87\times10^6\pm1.05$; P=0.01) (Figure 3). Based on the results sperm morphology did not change significantly in our study (Figure 4).

Evaluation of DNA fragmentation

Comparison the mean percentage of DFI before and after the intervention showed that the use of supplements and supplements with exercises and also exercises have significant reduced DFI (DPP: 17.578±2.07% vs 12.57±1.63%; P=0.016, ginger: 19.62±1.01% vs 13.50±0.73%; P=0.007, DPP+exercise: 23.25±2.51% vs 15.75±1.84%; P=0.025, ginger+exercise: 25.50±2.29% vs 15.25±1.29%; P=0.008, exercise: 25.62±2.29% vs 18.25±1.70%; P=0.006 and control: 20.85±2.21% vs 20.28±1.99%; P=0.68) (Figure 5).

Comparing hormonal profile before and after the intervention

All hormonal parameters of patients under study are summarized in Table 4. Our data showed that mean values of FSH and TT increased after consuming the DPP or ginger or doing exercise alone or along with supplements but The level of LH showed a significant increase in all groups, except for the exercise and control groups (Table 4).

Discussion

In recent years, antioxidants, nutritional regimens, and several medicinal plants have been proposed as complementary treatments to solve fertility problems in infertile couples. Some of these herbs improve sperm count and motility, while others affect the secretion of hormones by the testicles [23]. Flavonoids and phenolic compounds

Table 2. Comparing age, duration of infertility and height, before and after the intervention

Variables	Mean±SEM		P
	Before	After	
Duration of infertility (y)	2.4±0.2	2.4±0.2	0.234
Age (y)	34.6±2.33	34.6±2.33	0.324
Hight (cm)	166.43±3.33	166.43±3.33	0.111

Notes: Analysis was performed by the paired t-test.

Table 3. Comparing BMI before and after the intervention

Group/Variables	Mean±SEM		P
	Before the Intervention	BMI After the Intervention	
DPP	29.1±0.23	29.1±0.34	NS
Ginger	28.9±0.14	29.03±0.22	NS
DPP+exercise	26.65±1.60	24.13±1.53	0.001
Ginger+exercise	26.68±1.34	24.81±1.20	0.003
Exercise	29.23±3.08	27.15±2.98	0.002
Control	28.87±1.06	28.89±1.87	NS

DPP: Date palm pollen; NS: Not specified.

Notes: Analysis was performed by the paired t-test.

in some plants act as strong antioxidants against oxygen free radicals. They actually protect sperm against free radicals and improve sperm quality and fertility parameters [24]. Meanwhile, according to the WHO, despite the widespread use of herbal medicines, scientific knowledge about their properties has not yet reached the optimal level, and studies on herbal medicines should continue.

On the other hand, resistance training has been linked to a modulation in male infertility through antioxidant and anti-inflammatory pathways [1]. Since recent guidelines for oxidative stress-derived male infertility propose that lifestyle management should be done in a way that minimizes the causes of oxidative stress, exercise is regarded as one of the suggested therapies [25]. However, there is still debate regarding whether exercise enhances semen quality. Therefore, given the limited scientific research on medicinal herbs, as well as conflicting findings about exercise's impact on male fertility, the effects of oral DPP and ginger consumption without or with resistance training were assessed in infertile men with OAT in this study.

The obtained sperm parameter results showed that the sperm count and motility significantly increased after receiving the respective interventions in the experimental groups of DPP, ginger, DPP+exercise and ginger+exercise (P≤0.05). In contrast, these parameters did not significantly increase in the control and exercise groups (P>0.05). However, only the two groups receiving DPP and ginger showed a significant improve-

Table 4. Comparing hormonal profile before and after the intervention

Parameters	Mean±SEM		P	Mean±SEM		P	Mean±SEM		P
	FSH (mUL/mL)			LH (mUL/mL)			TT (ng/mL)		
	Before	After		Before	After		Before	After	
DPP	3.06±0.53	4.27±0.66	0.001	3.29±0.28	4.04±0.46	0.02	3.54±0.22	4.29±0.22	0.001
Ginger	3.47±0.62	4.65±0.66	0.001	3.16±0.13	4.1±0.20	0.001	3.01±0.20	3.77±0.23	0.004
DPP+exercise	3.26±0.47	4.34±0.45	0.001	3.25±0.25	3.96±0.32	0.04	3.01±0.27	3.55 ±0.30	0.023
Ginger+exercise	3.03±0.64	4.08±0.71	0.001	3.46±0.28	4.14±0.30	0.003	3.07±0.39	3.76±0.33	0.001
exercise	2.67±0.69	3.27±0.80	0.012	3.33±0.24	3.64±0.20	0.06	3.21±0.34	3.64±0.32	0.013
Control	2.92±0.78	2.87±0.75	0.45	3.35±0.26	3.39±0.26	0.33	3.57±0.52	3.54±0.53	0.44

Abbreviations: LH: Luteinizing hormone; FSH: Follicle stimulating hormone; TT: Total testosterone; DPP: Date palm pollen.

Notes: Analysis was performed by the paired t-test.

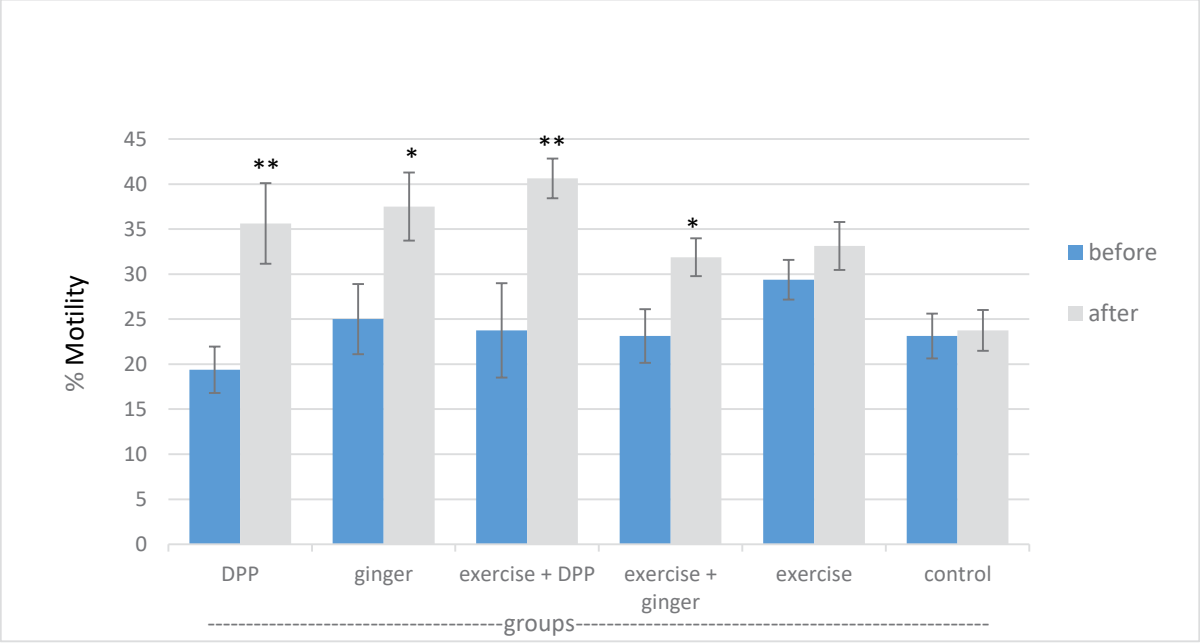

Figure 1. Comparing total motility between study groups before and after the intervention
*P<0.05, **P<0.001.

ment in the rate of sperm progressive motility (P≤0.05). These findings are in line with a clinical trial in which 40 infertile men received 120 mg/kg of DPP in a gelatin capsule once a day for two months, resulting in a significant increase in sperm count, total and progressive motility, and overall sperm quality [15]. Additionally, in a recent clinical trial, 250 mg of DPP was administered twice a day for two months in men with OAT. These men also showed a notable improvement in both total and progressive sperm motility [26].

It has been discovered that ginger has a positive impact on the reproductive performance of male rats, and this finding is supported by other studies showing an increase in sperm count, motility, and testosterone level along with a decrease in malondialdehyde activity. Additionally, similar results regarding the effect of ginger on

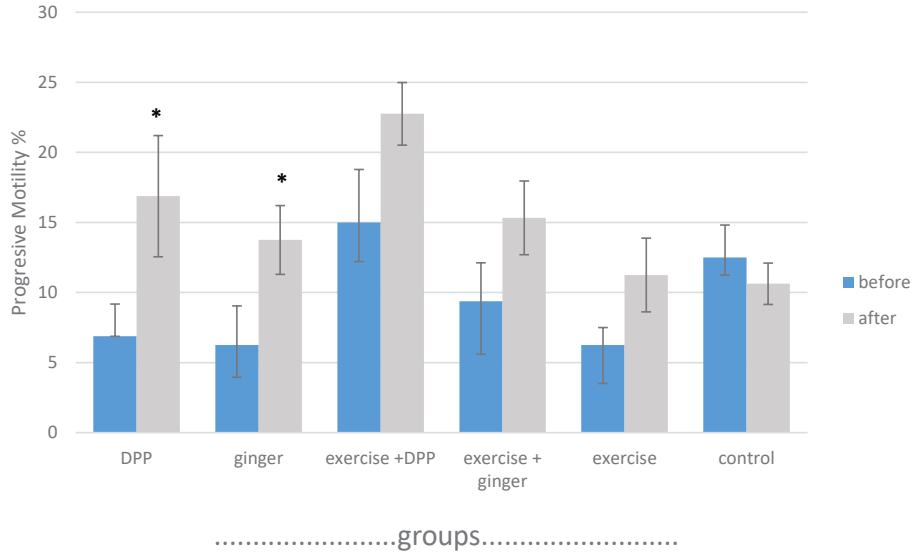

Figure 2. Comparing progressive motility between study groups before and after the intervention
*P<0.05, **P<0.001.

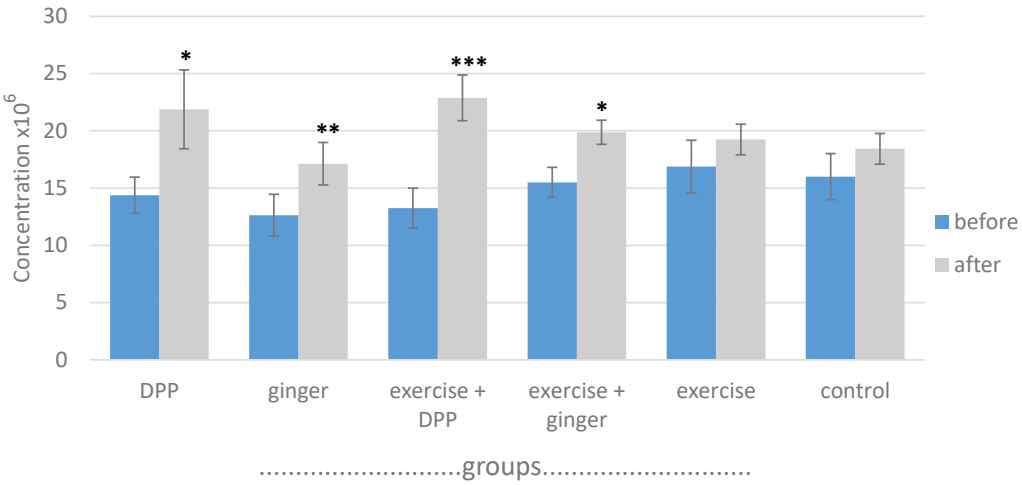

Figure 3. Comparing sperm concentration between the study groups before and after the intervention
*P<0.05, **P<0.001.

the count and motility parameters in animal models have also been previously reported [27-30]. Several studies have investigated how ginger affects human fertility [31, 32]. Hosseini et al. investigated how ginger extract affects infertile men's sperm DNA fragmentation and fertility potential [32]. In this trial, capsules containing 250 mg of ginger powder were taken twice daily for two months. The findings demonstrated that the proportion of sperm DNA damage was significantly lower in the ginger extract-treated infertile patients than in the control group. Contrary to the results of the present study, there was no statistically significant change in the total number and motility of sperm between the treatment and control groups [32].

The results in the exercise group are generally in line with those of earlier research. For instance, in a study, 556 infertile men were randomly assigned to resistance and aerobic exercise for 60 minutes three times a week, and they were compared to men who did not exercise for 24 weeks. Exercise resulted in weight loss and decreased belly fat in these individuals, as well as improved semen parameters, decreased sperm DNA fragmentation, oxidative stress, and pro-inflammatory cytokines, and increased pregnancy and live birth rates [33].

The anti-apoptotic properties of palm pollen in the genitourinary system, particularly in the testis and prostate, can be attributed to improving sperm motility in the current study [34]. In fact, palm pollen decreases the

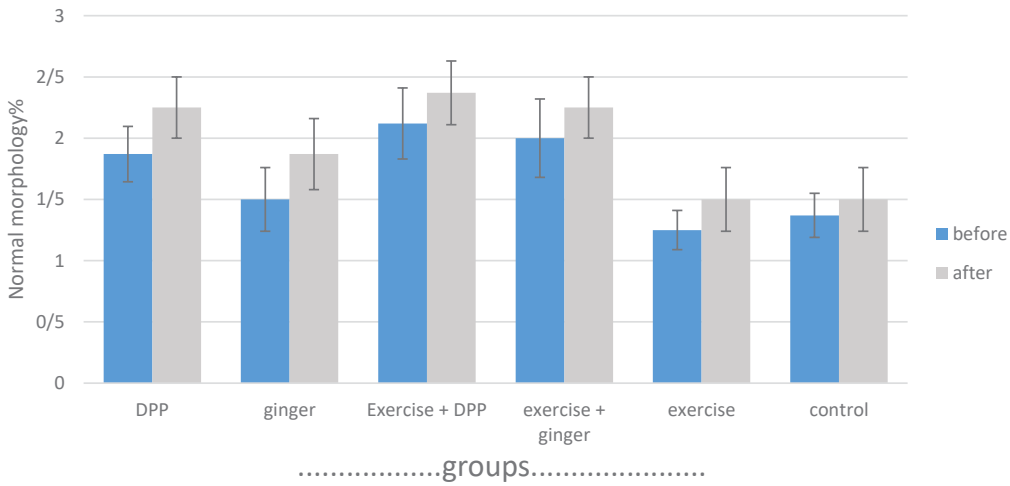

Figure 4. Comparing normal morphology between the study groups before and after the intervention
*P<0.05, **P<0.001.

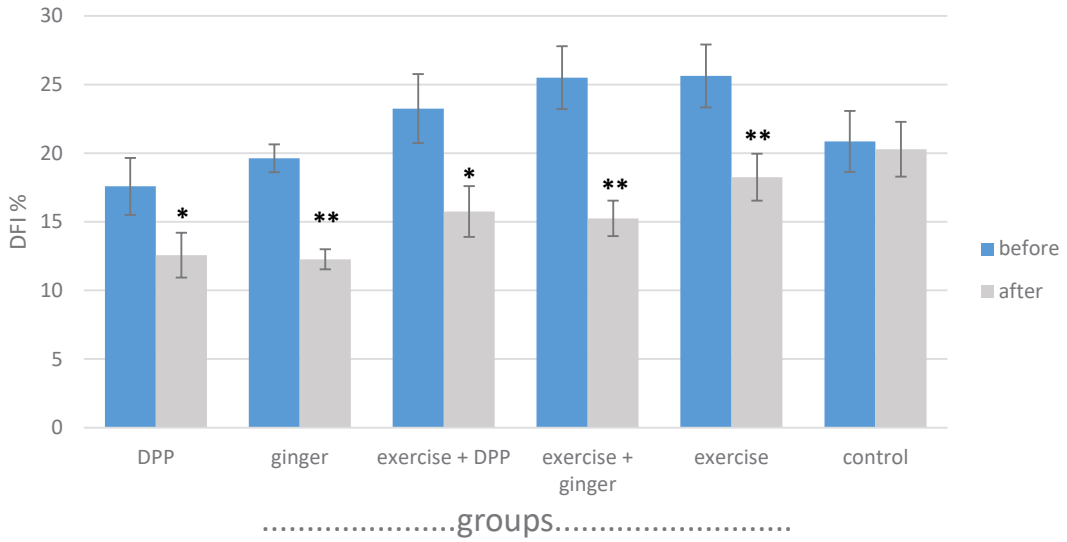

Figure 5. Comparing DFI before and after the intervention
*P<0.05, **P<0.001.

denaturation of sperm DNA, which results in apoptosis and, subsequently, higher sperm DNA quality. Much research on the role of apoptosis in male infertility reveals a connection between elevated cell death and reproductive issues [35]. Because antioxidants are crucial for preserving semen from ROS and can enhance basic sperm parameters in patients with idiopathic OAT, the antioxidant activity of palm pollen likely contributed to the enhanced sperm motility parameters in the current study [36]. Vitamins E and C have antioxidant properties and an inhibitory effect on ROS generation, also are found in palm pollen [37-39]. The regulation of sperm DNA fragmentation, as demonstrated in the current study, may be one of the factors driving the enhancement of sperm motility with palm pollen treatment. This, in turn, enhances the index of sperm DNA fragmentation and chromatin integrity by lowering sperm DNA damage [40, 41].

On the other hand, the presence of vitamins C and E in DPP can considerably boost glutathione levels, superoxide dismutase levels, and catalase activity while lowering levels of total protein, nitric oxide, and products of lipid peroxidation. This condition explains why sperm motility parameters in patients with OAT improves following DPP administration [42-44]. Additionally, the effect of DPP on sperm tail abnormalities, which is related to sperm motility [45], can be used to explain this significant improvement in sperm motility. The sperm tail (flagella), which contains the primary components regulating sperm movement, gives sperm motility [46]. In addition, this significant improvement in sperm motility can be explained by the effect of DPP on sperm tail abnormalities. DPP reduces the number of sperm with tail abnormalities, which is related to sperm motility [45]. Additionally, due to the antioxidant properties of primary active phenolic compounds extracted from ginger, it has been shown that ginger enhances sperm motility in treated groups of animal models [23].

The percentage of sperm DNA fragmentation in various experimental groups was another variable examined in this study. In light of the earlier discussion regarding the impact of palm pollen and ginger on sperm motility, the results obtained in this study are fully justified, as a significant reduction in DNA fragmentation was seen in all experimental groups ($P \leq 0.05$).

The amount of LH, FSH and testosterone hormones also increased in all experimental groups following the intervention, which was statistically significant ($P \leq 0.05$), with the exception of LH in the group having exercise alone. These findings are consistent with those of earlier research, which revealed that palm pollen elevates testosterone, LH, and FSH levels in males [15]. By preventing the creation of free radicals, inhibiting oxidative chain reactions, lowering oxidative stress, and altering the levels of sex hormones and gonadotropin hormones (LH and FSH), ginger enhances the quality of semen and boosts sperm fertility [47]. Additionally, it has been demonstrated that participating in sports of moderate intensity increases male fertility [48].

Numerous randomized controlled trials have linked both resistance training and aerobic exercise of moderate and high intensity to improvements in sperm param-

eters in infertile men, suggesting an improved testicular function in these patients [49]. In fact, regular exercise raises testosterone and lowers estrogen levels in humans. Exercise directly affects male fertility by raising levels of blood sex hormones LH, FSH and testosterone, which are closely related to the characteristics of semen.

Conclusion

In conclusion, the findings of this clinical trial study support the beneficial and protective effects of DPP, ginger, and resistance training on sperm parameters, sperm DNA fragmentation rate, and sex hormones. However, it appears that conducting clinical trials with more patients in a multicenter manner can provide additional and useful information, especially in light of the contradictory results that exist, particularly regarding sports activity and its impact on male sexual performance.

Study limitations

One of the restrictions of this study was the number of participants who must undergo 24 sessions of resistance training. So, it was important to identify these people and guarantee their dedication to attend all sessions and finish the movements. Furthermore, doing a study with a bigger sample size will produce more generally applicable and accepted results.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the University of Qom (Code: IRCT20191210045681N2). Informed consent was obtained from all participants.

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Authors contribution's

Conceptualization: Elham Asa, Amir Delshad, Fereshte Salimi, Atefeh Verdi and Mehdi Azadpour; Data acquisition: Elham Asa and Fereshte Salimi; Data analysis and interpretation: Elham Asa; Writing: Elham Asa and Hoda Fazaeli; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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