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EFFECTS OF CLOMIPHENE CITRATE DOSAGE AND EXERCISE MODALITY ON SPERM QUALITY IN HYPO-GONADAL MEN

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Abstract

Hypogonadism in men is a clinical condition characterized by insufficient production of testosterone leading to infertility. The aim of this study is to investigate the combined effects of varying clomiphene citrate (CC) dosages and different exercise modalities (aerobic vs. resistance training) on sperm quality parameters, including sperm count, motility, and morphology, hormonal changes and relationship between these attributes in hypogonadal men. This randomized, controlled trial involved 120 hypogonadal men aged 20-45, who were assigned to one of four groups to receive varying doses of CC (25 mg or 50 mg) combined with either aerobic or resistance training for 12 weeks. Sperm quality, hormonal levels, and quality of life were assessed at baseline and post-intervention. It was revealed that sperm concentration, motility, and morphology improved with increasing CC dosage, with the greatest improvements observed in the 50 mg CC + resistance training group. Testosterone levels increased significantly in all groups, with the highest increase in the 50 mg CC + resistance training group, while estradiol levels decreased modestly. Both LH and FSH levels were positively influenced by higher CC doses and resistance training, while prolactin levels decreased significantly. MIQoL scores also improved across all groups, with the greatest enhancement in the high-dose CC + resistance training group. Moreover, strong positive correlations were found between LH, FSH, and sperm quality parameters, while prolactin showed negative correlations with sperm concentration, motility, and morphology. CC when combined with resistance training, enhance sperm quality parameters, testosterone levels, and overall male infertility quality of life. Therefore, it is recommended as a potential therapeutic approach for improving male reproductive health, particularly in individuals experiencing fertility challenges.

Keywords: *Sperm quality, Hormonal changes, Infertility, Quality of life.*

Introduction

Hypogonadism in men is a clinical condition characterized by insufficient production of testosterone, sperm, or both. This condition often arises due to dysfunctions in the hypothalamic-pituitary-gonadal (HPG) axis [1]. It can manifest as primary hypogonadism, where testicular failure leads to an inadequate response to luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as stated by Ma et al. [2]. Alternatively, secondary hypogonadism occurs from hypothalamic or pituitary dysfunction, resulting in insufficient secretion of LH and FSH [3]. Both forms of hypogonadism lead to reduced testosterone levels, diminished sperm count, and compromised fertility, highlighting the crucial hormonal balance necessary for normal male reproductive health. The prevalence of hypogonadism varies depending on age, lifestyle factors, and underlying health conditions. Among older men, testosterone deficiency becomes increasingly common, though its occurrence can be significant even in younger populations, especially when considering factors such as obesity, metabolic syndrome, and chronic illnesses. One of the indicators of male hypogonadism is low serum testosterone levels [4]. Clinically, this deficiency manifests in a wide range of symptoms that can impact both reproductive and non-reproductive health. On the reproductive front, men with hypogonadism often suffer from impaired sperm production, or oligospermia, contributing to male infertility. Testosterone plays a crucial role in spermatogenesis by stimulating Sertoli cells within the testes [5]; thus, low levels of this hormone directly affect sperm quality and motility. Long-term testosterone deficiency is associated with several metabolic disturbances, including insulin resistance, dyslipidemia, and increased fat mass [6], further exacerbating the risk of cardiovascular diseases and osteoporosis. Therefore, hypogonadism is not merely a reproductive disorder but has systemic effects, making it critical to recognize and address early to prevent broader health complications.

Clomiphene Citrate (CC) is a selective estrogen receptor modulator (SERM) that has gained prominence as an alternative treatment for male hypogonadism, particularly in patients where maintaining fertility is a priority. Testosterone replacement therapy (TRT) has traditionally been the primary treatment for hypogonadism [7]. However, a major drawback of TRT can suppress endogenous testosterone production and decrease sperm count. In contrast, CC avoids this issue by blocking estrogen receptors in the hypothalamus and negative feedback normally exerted by circulating estrogens on the hypothalamic-pituitary-gonadal (HPG) axis [8]. This action stimulates the release of gonadotropin-releasing hormone (GnRH) from the hypothalamus, which in turn promotes the secretion of LH and FSH from the anterior pituitary. The increase in LH enhances testosterone production in the Leydig cells, while FSH supports spermatogenesis through its effect on Sertoli cells within the seminiferous tubules. By enhancing endogenous testosterone production, CC can improve testosterone levels without suppressing the HPG axis, preserving testicular function and sperm production [9]. Additionally, CC is generally well-tolerated, with fewer side effects, such as mild mood changes, headaches, and visual disturbances, which are often reversible upon discontinuation [10]. Notably, CC has potential as a long-term therapy, providing sustained improvements in testosterone levels and spermatogenesis without the risk of testicular atrophy or dependence on exogenous hormones. Thus, CC serves as a fertility-sparing alternative to TRT, making it an attractive option for many men with hypogonadism.

Exercise is widely recognized as a critical factor in promoting overall health, including reproductive function. Various exercise modalities, including aerobic and resistance training, have distinct impacts on male reproductive health, particularly with respect to testosterone levels and sperm quality. Physical exercise, particularly when performed regularly, significantly influences hormonal regulation and the HPG axis, thereby impacting male reproductive health [11]. Aerobic exercise, characterized by sustained cardiovascular activities, has been shown to boost testosterone levels when performed at moderate intensity. Regular aerobic training can also improve sperm motility, count, and morphology by enhancing cardiovascular function and reducing oxidative stress in the reproductive system [12]. Similarly, resistance or strength training, typically involving high-intensity, short-duration exercises like weightlifting, has been associated with more robust increases in testosterone levels [13]. Resistance training stimulates the release of anabolic hormones, promoting testosterone secretion, and potentially benefiting spermatogenesis [14], although the relationship between exercise intensity, volume, and sperm quality is complex. In hypogonadal men, exercise improves general health and may have synergistic effects on hormonal regulation. When combined with treatments like CC, exercise can further enhance testosterone levels and positively impact sperm parameters. Both aerobic and resistance exercises improve insulin sensitivity, reduce body fat, and modulate inflammatory markers, all of which can indirectly influence testosterone production and reproductive function. Understanding how different exercise modalities interact with pharmacological treatments like CC is crucial for developing comprehensive interventions for men with hypogonadism.

Despite evidence on the individual effects of exercise and CC on male reproductive health, the combined impact of these interventions remains underexplored. Few studies have examined how CC dosage interacts with exercise modalities (aerobic vs. resistance training) to influence sperm quality in hypogonadal men. While both treatments independently enhance testosterone production and spermatogenesis, their potential synergistic effects are unclear. Additionally, there is a lack of dose-response studies on the optimal CC dosage alongside exercise. This study aims to investigate how varying CC doses, combined with different exercise types, affect sperm count, motility, and morphology, addressing gaps in the current literature.

Materials and Methods

Study Design

This study is a randomized, controlled trial designed to evaluate the combined effects of CC dosage and exercise modality on sperm quality in hypogonadal men. The study population comprises 120 men, aged 20-45, with clinically confirmed hypogonadism and a history of infertility. Participants were randomly assigned to one of four treatment groups, each receiving different combinations of CC dosages and exercise modalities over a 12-week period.

Study Population

Inclusion Criteria

The study focuses on males aged 20 to 45 who have been diagnosed with hypogonadism, characterized by total testosterone levels below 300 ng/dL. Participants must exhibit clinical symptoms of hypogonadism, such as fatigue, low libido, and reduced muscle mass. Additionally, they should have a history of infertility, defined as the inability to conceive after 12 months of unprotected intercourse. Eligible subjects must have a normal karyotype, with no evidence of testicular cancer, and they must not have undergone testosterone replacement therapy (TRT) within the last six months. This selection criteria aims to ensure a specific and relevant population for investigating potential treatment options.

Exclusion Criteria

Men with azoospermia, untreated varicocele, severe medical comorbidities such as liver or kidney disease, or a history of substance abuse will be excluded from the study. Additionally, individuals who have used medications known to affect hormone levels or sperm quality, including anabolic steroids, will not be eligible for participation. Furthermore, any man who has participated in an infertility treatment program within the last six months will also be excluded from the study. These exclusion criteria are established to ensure that the study population is as homogenous as possible and to minimize confounding factors that could influence the outcomes of the research.

Randomization and Group Allocation

Participants in the study were randomly assigned to one of four groups, with 30 participants per group. Group A received low-dose CC (25 mg) combined with aerobic exercise, while Group B was administered low-dose CC (25 mg) along with resistance training. Group C received high-dose CC (50 mg) in conjunction with aerobic exercise, and Group D was assigned high-dose CC (50 mg) combined with resistance training. Participants in Groups A and B received 25 mg of CC daily for 12 weeks, whereas those in Groups C and D received 50 mg daily for the same duration. Aerobic exercise for Groups A and C consisted of 150 minutes of moderate-intensity activities, such as jogging, cycling, or swimming, performed over five sessions of 30 minutes each week, with participants using heart rate monitors to maintain moderate intensity (50-70% of maximum heart rate). In contrast, participants in Groups B and D engaged in three resistance training sessions weekly, targeting major muscle groups with 8-10 exercises per session, including squats, deadlifts, bench presses, and rows, performed in 3 sets of 8-12 repetitions at 70-80% of their one-repetition maximum (1RM). All exercise modalities were supervised and monitored by fitness trainers to ensure adherence to the protocols, with weekly feedback provided to participants. A computer-generated randomization sequence was utilized to allocate participants to each group, ensuring equal distribution and minimizing selection bias.

Attributes to be measured

Sperm Quality Parameters

Sperm quality was assessed via semen analysis at baseline (week 0) and after the 12-week intervention (week 12). Semen samples were collected after 72 hours of sexual abstinence and analyzed in a laboratory according to WHO guidelines. The following parameters were measured:

Sperm concentration (million/mL)

Sperm motility percentage (progressive and total)

Sperm morphology (percentage of morphologically normal sperm)

Hormonal Levels and Quality of Life

Testosterone and Estradiol Level

Blood samples were collected at baseline and week 12 to measure total testosterone and estradiol levels. Hormonal assays were performed using chemiluminescent immunoassays (CLIA) [15].

LH, FSH and Prolactin levels

Blood samples for measuring luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin levels were collected from participants at baseline (week 0) and after the 12-week intervention (week 12), following an overnight fast to minimize variability. Serum was separated via centrifugation and stored at -20°C until analysis. Hormone levels were measured using chemiluminescent immunoassays (CLIA) [16], with each hormone analyzed using separate assay kits according to the manufacturer's instructions. The optical density was measured using a microplate reader to calculate hormone concentrations based on a standard curve. Quality control samples were included in each assay run to ensure accuracy and precision.

Quality of Life

Participants' quality of life was assessed using the Male Infertility Quality of Life (MIQoL) questionnaire after the intervention. This validated tool assesses the emotional, social, and physical well-being of men undergoing infertility treatment.

Monitoring and Compliance

Participants attended weekly check-ins to monitor medication adherence, exercise participation, and general health. Compliance was assessed through pill counts, exercise logs, and attendance records. Adverse effects, if any, were documented at each visit.

Statistical Analysis

Analysis of variance (ANOVA) was used to evaluate the main effects of CC dosage (25 mg vs. 50 mg) and exercise modality (aerobic vs. resistance training) on primary sperm quality parameters (sperm concentration, motility, and morphology). Interaction effects between dosage and exercise modality were also assessed. Where significant effects were observed, least significant test was performed to identify specific differences between the groups.

Changes in testosterone and estradiol levels, as well as MIQoL scores, were analyzed using paired t-tests and repeated measures ANOVA. Statistical significance was set at $p < 0.05$, and all analyses were performed using SPSS (version 25).

Ethical Considerations

The study protocol was approved by the Institutional Review Board (IRB) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Results

The effect of different dosages of clomiphene citrate and exercise modalities on sperm quality parameters, including sperm concentration, motility, and morphology, was investigated (Table 1). Sperm concentration was significantly influenced by both the CC dosage and the type of exercise (LSD = 3.5). The lowest concentration was observed in the group receiving 25 mg CC combined with aerobic exercise (20.5 ± 4.3 million/mL). Sperm concentration increased slightly in the group performing resistance training with 25 mg CC (22.1 ± 3.9 million/mL). A higher dose of CC (50 mg) combined with aerobic exercise resulted in a further increase in sperm concentration (25.8 ± 5.1 million/mL), while the highest concentration was observed in the group receiving 50 mg CC combined with resistance training (28.3 ± 4.7 million/mL). Sperm motility was also significantly affected by the treatment combinations (LSD = 4.2). The lowest motility was recorded in the group receiving 25 mg CC with aerobic exercise (45.2 ± 5.4%). A slight improvement was observed with resistance training at the same dose (48.3 ± 4.6%). Increasing the CC dosage to 50 mg improved motility in the aerobic exercise group (55.1 ± 6.2%), with the highest motility observed in the 50 mg + resistance training group (60.5 ± 5.8%). Moreover, sperm morphology was significantly improved with increasing CC dosage and resistance training (LSD = 3.9). The group receiving 25 mg CC with aerobic exercise had the lowest percentage of normal sperm morphology (30.5 ± 5.1%).

Table 1: Effect of clomiphene citrate dosage and exercise modality on sperm quality.

Parameter	Treatment combination	Mean ± SD	LSD value
Sperm Concentration (million/mL)	25 mg + Aerobic Exercise	20.5 ± 4.3	3.5
	25 mg + Resistance Training	22.1 ± 3.9	
	50 mg + Aerobic Exercise	25.8 ± 5.1	
	50 mg + Resistance Training	28.3 ± 4.7	
Sperm Motility (%)	25 mg + Aerobic Exercise	45.2 ± 5.4	4.2
	25 mg + Resistance Training	48.3 ± 4.6	
	50 mg + Aerobic Exercise	55.1 ± 6.2	
	50 mg + Resistance Training	60.5 ± 5.8	
Sperm Morphology (%)	25 mg + Aerobic Exercise	30.5 ± 5.1	3.9
	25 mg + Resistance Training	32.8 ± 4.4	
	50 mg + Aerobic Exercise	37.6 ± 6.1	
	50 mg + Resistance Training	40.2 ± 5.5	

LSD (least significant difference at 0.001, 0.01 and 0.05).

Change in testosterone and estradiol levels

The study evaluated the effects of CC (CC) dosage and exercise modality on testosterone and estradiol levels over a 12-week period. Both low and high doses of CC combined with either aerobic or resistance training resulted in significant changes in these hormone levels, with notable differences between the treatment groups (Table 2). At baseline, testosterone levels ranged from 285 ± 28 ng/dL to 295 ± 32 ng/dL across the four groups. After 12 weeks of intervention, all treatment groups exhibited significant increases in testosterone levels ($p < 0.01$). In the low-dose CC groups, aerobic exercise (Group A) led to an increase from 290 ± 30 ng/dL to 387 ± 35 ng/dL, while resistance training (Group B) resulted in a larger increase from 295 ± 32 ng/dL to 410 ± 33 ng/dL. Similarly, the high-dose CC groups showed pronounced increases in testosterone. Aerobic exercise (Group C) increased testosterone levels from 285 ± 28 ng/dL to 419 ± 26 ng/dL, while resistance training (Group D) produced the highest rise in testosterone, from 292 ± 29 ng/dL to 430 ± 35 ng/dL.

Estradiol levels also changed significantly during the 12-week intervention ($p < 0.05$). Baseline estradiol concentrations ranged from 39 ± 5 pg/mL to 42 ± 7 pg/mL. After 12 weeks, all groups demonstrated a reduction in estradiol levels. In Group A, estradiol decreased from 40 ± 5 pg/mL to 35 ± 4 pg/mL following low-dose CC and aerobic exercise. Group B, which combined low-dose CC with resistance training, saw a decrease from 41 ± 6 pg/mL to 36 ± 5 pg/mL. Among the high-dose CC groups, estradiol dropped from 39 ± 5 pg/mL to 34 ± 4 pg/mL in the aerobic exercise group (Group C), and from 42 ± 7 pg/mL to 37 ± 5 pg/mL in the resistance training group (Group D). Although reductions in estradiol were observed across all groups, the changes were relatively modest in comparison to the testosterone increases. Aerobic exercise led to slightly greater decreases in estradiol levels compared to resistance training.

Table 2: Effect of clomiphene citrate dosage and exercise modality on Testosterone and Estradiol.

Group	*Baseline Testosterone (ng/dL)*	*Week 12 Testosterone (ng/dL)*	*p-value (Testosterone)*	*Baseline Estradiol (pg/mL)*	*Week 12 Estradiol (pg/mL)*	*p-value (Estradiol)*
Group A: Low-dose CC + Aerobic Exercise	290 ± 30	387 ± 35	< 0.01	40 ± 5	35 ± 4	< 0.05
Group B: Low-dose CC + Resistance Training	295 ± 32	410 ± 33	< 0.01	41 ± 6	36 ± 5	< 0.05
Group C: High-dose CC + Aerobic Exercise	285 ± 28	419 ± 26	< 0.01	39 ± 5	34 ± 4	< 0.05
Group D: High-dose CC + Resistance Training	292 ± 29	430 ± 35	< 0.01	42 ± 7	37 ± 5	< 0.05

LSD (least significant difference at 0.05).

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels

The interactive effects of CC dosage (25 mg and 50 mg) and exercise modality (aerobic vs. resistance training) on luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were evaluated. The results, as illustrated in the graph, indicate significant interactions between these variables (Figure 1). At the 25 mg dosage, aerobic exercise led to a lower LH level compared to resistance training, with values of approximately 6.0 mIU/mL and 7.2 mIU/mL, respectively. When the dosage was increased to 50 mg, both exercise types showed an increase in LH levels. However, resistance training induced a larger rise, with LH levels reaching about 8.0 mIU/mL, while aerobic exercise resulted in a lower value, around 6.5 mIU/mL. Similarly, for FSH levels, the 25 mg dose combined with resistance training resulted in higher FSH levels (approximately 4.0 mIU/mL) compared to aerobic exercise (around 3.2 mIU/mL). With the 50 mg dosage, resistance training continued to show a greater increase in FSH levels, reaching about 5.0 mIU/mL, while aerobic exercise induced a more moderate increase, with FSH levels at approximately 3.7 mIU/mL.

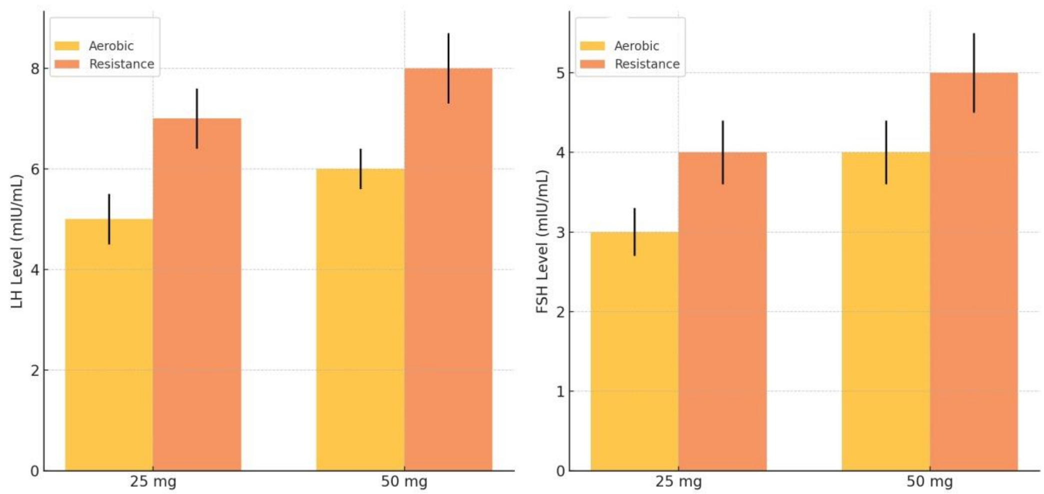

Figure 1Interactive effect of clomiphene citrate dosage and exercise modality on LH and FSH hormones.

Prolactin levels

The interactive effects of CC dosage and exercise modality on prolactin levels are depicted in the graph (Figure 2). At the 25 mg dose, aerobic exercise resulted in higher prolactin levels (approximately 13 ng/mL) compared to resistance training (around 12 ng/mL). As the dosage increased to 50 mg, prolactin levels decreased for both exercise modalities, with aerobic exercise showing a level of about 10 ng/mL and resistance training resulting in an even lower level, approximately 8.5 ng/mL.

Figure 2 Effect of clomiphene citrate dosage and exercise modality on prolactin levels

The effect of CC dosage and exercise modality on the MIQoL (Male Infertility Quality of Life) score was statistically significant across all groups. At baseline, the MIQoL scores ranged from 3.4 to 3.7, with no significant differences between groups (Table 3). Post-intervention, improvements in MIQoL scores were observed in all groups. Group A (low-dose CC + aerobic exercise) showed an increase from 3.5 ± 1.2 to 4.4 ± 1.1 ($p < 0.05$), while Group B (low-dose CC + resistance training) improved from 3.6 ± 1.3 to 4.8 ± 1.0 ($p < 0.05$). Similarly, Group C (high-dose CC + aerobic exercise) increased from 3.4 ± 1.1 to 4.2 ± 1.2 ($p < 0.05$), and Group D (high-dose CC + resistance training) showed an improvement from 3.7 ± 1.0 to 5.0 ± 1.1 ($p < 0.05$).

Table 3: Effect of clomiphene citrate dosage and exercise modality on MIQoL Score.

GROUP	BASELINE MIQOL SCORE (MEAN ± SD)	POST-INTERVENTION MIQOL SCORE (MEAN ± SD)	P-VALUE
GROUP A	3.5 ± 1.2	4.4 ± 1.1	< 0.05
GROUP B	3.6 ± 1.3	4.8 ± 1.0	< 0.05
GROUP C	3.4 ± 1.1	4.2 ± 1.2	< 0.05
GROUP D	3.7 ± 1.0	5.0 ± 1.1	< 0.05

The MIQoL questionnaire used a Likert scale for responses, with a range from 1 (Never) to 5 (Always), where higher scores indicate a greater perceived impact of infertility on quality of life.

Correlation between sperm quality and hormonal levels

The correlation matrix presents the relationships between luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin, and sperm quality parameters, including sperm concentration, motility, and morphology (Figure 3). LH and FSH showed a strong positive correlation (r = 0.99), suggesting that an increase in one hormone is closely associated with an increase in the other. Both LH and FSH were positively correlated with sperm concentration (r = 0.96 and r = 0.90, respectively), sperm motility (r = 0.96 and r = 0.91, respectively), and sperm morphology (r = 0.96 and r = 0.90, respectively), indicating that higher levels of these hormones are associated with improvements in sperm quality parameters. Conversely, prolactin exhibited strong negative correlations with all measured parameters. Specifically, prolactin had a significant inverse relationship with LH (r = -0.99), FSH (r = -0.95), sperm concentration (r = -0.99), sperm motility (r = -0.99), and sperm morphology (r = -0.99).

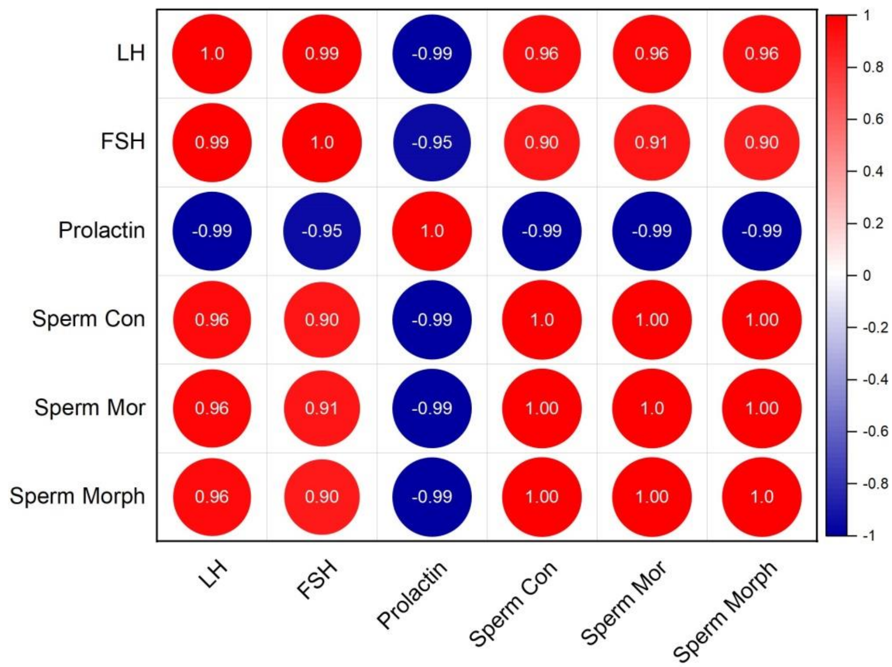

Figure 3 Correlation between hormonal levels and sperm quality under clomiphene citrate dosage and exercise modality.

Discussion

Our research revealed that both CC dosage and exercise modalities had strong impact on sperm quality parameters. The lowest sperm concentration was observed in the group receiving 25 mg CC combined with aerobic exercise, which is in line with reports suggesting that aerobic exercise can increase oxidative stress, potentially impairing spermatogenesis [17]. A slight improvement was observed in sperm concentration when resistance training was introduced with the same CC dosage. This finding aligns with evidence indicating that resistance exercise can mitigate oxidative stress and promote better sperm production due to its anabolic effects [18]. The increased sperm concentration at the higher dose of CC (50 mg) in both aerobic and resistance training groups underscores the dose-dependent effects of clomiphene on increasing gonadotropin levels, which is consistent with literature stating that higher doses of clomiphene stimulate testosterone production and spermatogenesis [19]. Sperm motility was similarly enhanced with increased CC dosage and resistance training. This mirrors findings from research highlighting the synergistic effects of CC in combination with resistance training, which enhances testosterone and antioxidant levels, thereby improving sperm motility. Moreover, the improvements in sperm morphology observed with increasing CC dosage and resistance training suggest that the anabolic effects of resistance exercise, in conjunction with CC's hormonal modulation that might have supported better sperm morphology, as previously reported [20].

After the intervention, all groups showed significant increases in testosterone levels ($p < 0.01$), particularly in those combining CC with resistance training, which led to the most pronounced increases. This rise in testosterone was consistent with previous studies, which indicated that CC enhanced endogenous testosterone production by stimulating gonadotropins, particularly when combined with resistance training, which is known to further amplify testosterone release. Research suggested that resistance training improved anabolic hormone responses, thus maximizing the effect of CC on testosterone levels [21]. In contrast, aerobic exercise also elevated testosterone levels, though the increases were less pronounced compared to resistance training. These findings were consistent with studies suggesting that aerobic exercise has a more modest impact on testosterone levels, likely due to its lower ability to induce muscle hypertrophy and stimulate anabolic hormone production compared to resistance training [22]. The study revealed significant reductions in estradiol levels across all groups, with aerobic exercise slightly outperforming resistance training in this regard. This finding aligns with literature indicating that CC acts as a selective estrogen receptor modulator (SERM), reducing estrogen production while enhancing androgen levels [23]. Moreover, aerobic exercise is known to lower estrogen levels through mechanisms such as improved metabolism and elimination of estrogen. The distinct hormonal responses observed may be attributed to the different physiological effects of each exercise modality, where resistance training effectively increases testosterone levels due to muscle hypertrophy and metabolic demands [24] while aerobic exercise promotes a more pronounced reduction in estradiol.

The study revealed that CC dosage and exercise modality significantly impacted LH and FSH levels. At the 25 mg dose, resistance training led to higher LH levels compared to aerobic exercise, suggesting a stronger hypothalamic-pituitary-gonadal (HPG) axis response. As the CC dose increased, LH levels rose further, highlighting the dose-dependent action of CC in enhancing gonadotropin secretion. Resistance training amplified this effect, particularly at higher doses. Similarly, FSH levels followed a similar trend, with resistance training resulting in more pronounced increases at both CC dosages. Resistance training, known for its muscle-building effects, appeared to enhance FSH levels more effectively than aerobic exercise. This suggests that resistance training may stimulate FSH, which plays a critical role in spermatogenesis and Sertoli cell function [25]. The greater increase in FSH levels with the higher 50 mg dose of CC further supports the notion that resistance training, in combination with CC, can optimize spermatogenic activity, as noted in previous literature. The interaction between CC dosage and exercise modality on prolactin levels suggests that higher CC doses effectively reduce prolactin secretion, particularly when combined with resistance training. This reduction is likely due to CC's role as a selective estrogen receptor modulator (SERM), which blocks estrogen's feedback on the hypothalamic-pituitary axis, thereby lowering prolactin levels. Resistance training, known for its androgen-boosting effects, further amplifies this reduction, as elevated testosterone is known to suppress prolactin release [26].

Aerobic exercise, while also lowering prolactin at higher CC doses, has a less pronounced effect due to its association with greater stress responses, which may slightly elevate prolactin.

The study's results demonstrate that CC dosage and exercise modality significantly impacted the Male Infertility Quality of Life (MIQoL) scores, with improvements observed across all treatment groups. At baseline, MIQoL scores were similar across groups, ranging from 3.4 to 3.7, indicating a uniform starting point for the intervention. Following the 12-week intervention, all groups experienced significant improvements in MIQoL scores ($p < 0.05$), with the magnitude of improvement varying based on the combination of CC dosage and exercise modality. Group B (low-dose CC + resistance training) and Group D (high-dose CC + resistance training) exhibited the most pronounced improvements. This suggests that resistance training, particularly when combined with either low or high doses of CC, may provide a greater psychological and quality of life benefit in male infertility contexts, likely due to its positive influence on testosterone levels and overall well-being [27].

In contrast, aerobic exercise combined with CC also led to significant but slightly smaller improvements in MIQoL. Group A (low-dose CC + aerobic exercise) saw increase while Group C (high-dose CC + aerobic exercise) also showed a rise from. Aerobic exercise can improve mood, reduce stress, and enhance general quality of life in men, although it may not be as effective as resistance training in addressing infertility-related concerns [28]. The greater improvements in MIQoL scores in the resistance training groups may be attributed to the anabolic and psychological benefits associated with resistance exercises, including enhanced self-esteem and reduced stress, both of which are critical factors in the overall experience of male infertility [29].

The correlation matrix provided insights into the hormonal regulation of sperm quality, emphasizing the roles of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin. The strong positive correlation between LH and FSH ($r = 0.99$) highlighted their synergistic role in regulating spermatogenesis, with LH stimulating Leydig cells to produce testosterone and FSH supporting Sertoli cells for sperm maturation. Furthermore, positive correlations of both LH and FSH with sperm concentration, motility, and morphology indicate that optimal levels of these hormones enhance sperm quality, aligning with their critical roles in promoting spermatogenesis [30]. In contrast, prolactin's strong negative correlations with LH, FSH, and all sperm quality parameters ($r = -0.99$) suggest that elevated prolactin levels negatively affect male reproductive health by suppressing the hypothalamic-pituitary-gonadal (HPG) axis, reducing LH and FSH secretion, and impairing testosterone production and spermatogenesis [31].

Conclusion

This study demonstrates that higher dosages of CC, particularly when combined with resistance training, significantly improve sperm quality parameters, testosterone levels, and MIQoL scores. Hormonal changes, including increased LH and FSH levels and decreased prolactin levels, were positively correlated with enhanced sperm concentration, motility, and morphology. These findings suggest that combining clomiphene citrate treatment with resistance exercise may offer an effective strategy for improving male reproductive health.

Conflict of interest

All the authors declared no conflict of interest.

Author's contributions

All the authors equally contributed to make this work possible.

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