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Effect of Resistance Training and Melatonin Supplementation on LH, FSH, PGF2a in Female With Primary Dysmenorrhea

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ABSTRACT

Background: Primary dysmenorrhea is associated with problems in women's life and hormonal disorders. This research aims to investigate the effect of resistance training and melatonin supplementation on luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prostaglandin F2α (PGF2a) in females with primary dysmenorrhea.

Materials and Methods: This is a randomized controlled clinical trial with a pre-test/post-test design. Sixty girls with primary dysmenorrhea recruited from a women's sports club in Mashhad, Iran, were randomly divided into four groups: Training+melatonin, training+placebo, melatonin, and control group. For supplementation, 10 mg of melatonin was taken daily using two 5 mg capsules, and the placebo was 10 mg of carbohydrates using two 5 mg capsules. Resistance training consisted of 50-60 minutes of weight training daily, three days a week, for eight weeks. Collected data were analyzed using repeated measures analysis of variance, followed by a post hoc test.

Results: The results showed a significant increase of FSH and LH levels in the training+melatonin group compared to other groups and in the training+placebo and melatonin groups compared to the control group. Moreover, there was a significant decrease in PGF2a in the melatonin group compared to other groups and in the training+placebo and training+melatonin groups compared to the control group.

Conclusion: The resistance training protocol used in this study is effective for women with primary dysmenorrhea. Melatonin, by affecting gonadotropin hormones as well as prostaglandin, overcomes the hormonal disorders caused by dysmenorrhea and can eliminate its symptoms.

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Introduction

Dysmenorrhea refers to feeling cramping pains caused by menstrual periods. Dysmenorrhea is one of the most important causes of school absenteeism among teenage girls and affects their academic performance and sports activities. Almost 20-90% of women of reproductive age suffer from this problem [1]. More than half of menstruating women endure pain caused by dysmenorrhea at least 1-2 days a month [2, 3]. Natural chemicals called prostaglandins, which are made in the uterine wall, are responsible for this pain. Primary dysmenorrhea begins when prostaglandin levels increase in the uterine wall. On the first day of menstruation, the level of prostaglandin reaches its highest level, and with the continuation of menstruation and the collapse of the uterine wall, its level decreases. Pain intensity also decreases with the reduction of prostaglandin level [4]. The menstrual cycle is divided into two follicular and luteal phases. The follicular phase includes menstruation, followed by the proliferation or increased thickness of the endometrium (the inner lining layer of the uterus). This phase lasts 10-14 days and begins on the first day of menstruation. When blood flow stops, the follicular phase begins and causes the uterine wall to grow and thicken to prepare the uterus for pregnancy [5]. Over the next two weeks, the follicle-stimulating hormone (FSH) level increases, causing the various ovarian follicles to grow and triple the size of the eggs. The FSH also sends signals to the ovary to start making estrogen, which stimulates luteinizing hormone (LH) to release one of the follicles on day 14 of the cycle and to release the largest egg into one of the fallopian tubes. This period before puberty lasts 14 days [6]. After ovulation, LH causes the corpus luteum to expand from the follicular cleft. A threefold increase in endometrial prostaglandins occurs from the follicular phase to the luteal phase, and a further increase occurs during menstruation. An increase in the prostaglandin level was found in the endometrial fluid of women with dysmenorrhoea, which was related to the severity of pain in them [7]. In mammals, prostaglandin F2α (PGF2α) is produced by the uterus when stimulated by oxytocin and when there is no implantation in the luteal phase. This substance acts on the corpus luteum and causes luteolysis, forms corpus albicans, and stops the production of progesterone. The function of PGF2α depends on the number of receptors in the corpus luteum membrane [8].

According to research results, regular exercise with sufficient intensity, by improving blood flow and increasing the release of endorphins, leads to a reduction in pain and symptoms of dysmenorrhea in young women and girls [9]. A study showed that regular physical activity is a useful and low-cost method to reduce and deal with the side effects of early dysmenorrhea symptoms in young girls [10]. On the other hand, there are contradictory results about the effect of exercises on primary dysmenorrhoea, which is probably due to the use of multiple training methods and factors such as the duration, intensity, and quality of the activity [2, 11].

Considering the role of hormones affecting ovulation and prostaglandin, which causes pain in women with dysmenorrhea, the use of melatonin supplements and resistance exercises with appropriate intensity and duration can be a good solution to eliminate the complications caused by this condition in women. In this study, melatonin was used as a countermeasure for the complications of dysmenorrhoea by reducing the levels of prostaglandin, which results in the absence of disturbances in LH and FSH. Although the evidence about the effects of exercises, especially resistance training, in women with dysmenorrhea is limited, different intensities and durations have reported different results. Therefore, a protocol was used in this study that can increase the mutual effects of supplementation and exercise. Therefore, this research aims to investigate the effect of resistance training and melatonin supplementation on LH, FSH, and PGF2a in females with primary dysmenorrhea.

Materials and Methods

This is a randomized controlled clinical trial with a pre-test/post-test design, conducted for eight weeks. The study population consists of women with a regular menstrual cycle from a women's sports club in Mashhad, Iran. Their medical history was checked, and those with a history of smoking, alcohol consumption, medical illness, using oral contraceptives, hormone replacement therapy, taking supplements containing tryptophan and folate (two substances used for melatonin production), and regular physical activity were excluded from the study. Those aged 18-25 years and single with regular and painful menstrual periods and no injury in the pelvis were included in the study. The regular menstruation period was defined as amenorrhea or menstrual cycles of 28-32 days in the past year. Then, based on the information obtained from the medical records, 60 women with primary dysmenorrhoea (according to the score of the menstrual distress questionnaire - short form) who met the criteria for entering the study were selected using purposive and convenience sampling methods. The sample size was estimated at 52 (13 in each group), according to previous studies, and considering a 95% confidence interval, 80% test power, and effect size of 0.5

using G*Power software, version 3.1.9.4. For more caution, it increased to 15 people per group. Before starting the exercise program, the participants' height, weight, and body mass index (BMI) were measured using a stadiometer and a scale. Before taking blood samples, subjects were reminded of important and necessary points about nutrition, physical activity, etc. to observe them. At the end, the subjects were randomly divided into study groups including training+melatonin (n=15), training+placebo (n=15), melatonin (n=15 people) and control (n=15).

The menstrual distress questionnaire - short form (MDQ- SF) with 16 items extracted from the questionnaire devised by Moss (1968) [12] was used to assess dysmenorrhea in participants. The validity and reliability of this questionnaire have been confirmed in a study in 2017 [13]. Blood sampling was done by an experienced lab expert. Fasting and resting blood samples (5 mL) were taken simultaneously before and after eight weeks of training intervention. All samplings were done in the follicular phase of the menstrual cycle. All subjects were fasting for at least 12 hours.

Resistance training consisted of 50-60 minutes of weight training every day, three days a week for eight weeks. Subjects in the training groups performed nine resistance exercises that were selected to put pressure on major muscle groups: Forearm with a barbell, chest press, dumbbell lateral raise, leg extension, back extension, sit-up, leg rotation, hip abduction, and hip adduction. These exercises were based on a circular protocol in 9 stations, including 2 sets in the first four weeks and 3 sets in the second four weeks, with a maximum of 10-12 repetitions at 30-65% of a maximum repetition in each station. There was a 2-3 minutes and 90 seconds of rest interval between sets and repetitions, respectively. Each training session ended with a 10-minute cool-down [1] The training intensity was increased by 5% every week except the last week. Subjects in the training+melatonin and melatonin groups received 10 mg of melatonin daily using two 5 mg capsules, while the training+placebo group received 10 mg carbohydrates using two 5 mg capsules. The melatonin supplement was taken before going to bed at night for seven consecutive days, starting on the first day of the menstrual period. It was explained to the women that they should not make any changes to their medications during the study period [13].

After collecting and entering data into SPSS software, version 22 they were analyzed using descriptive and inferential statistics. The normality of the data distribution was examined using the Shapiro-Wilk test. Since the data were normal, repeated measures analysis of variance (ANOVA) was used, followed by a post hoc test. $P<0.05$ was considered statistically significant.

Results

The descriptive data related to the demographic characteristics of the participants are shown in Table 1. There was no significant difference between the groups in demographic variables ($P>0.05$). The results of repeated measures ANOVA for LH showed significant between-group and within-group differences ($P<0.001$) (Figure 1). Bonferroni test showed that LH level increased significantly in the training+melatonin group compared to other groups and in training+placebo and melatonin groups compared to control group ($P<0.001$) (Table 2). The results of repeated measures ANOVA for FSH also showed significant between-group and within-group differences ($P<0.001$) (Figure 2). Bonferroni test showed that FSH level increased significantly in the training+melatonin group compared to other groups and in training+placebo and melatonin groups compared to control group ($P<0.001$) (Table 3). The results of repeated measures ANOVA for PGF2α also showed significant between-group and within-group differences ($P<0.001$) (Figure 3). Bonferroni test showed that PGF2α level decreased significantly in the training+melatonin group compared to other groups and in training+placebo and melatonin groups compared to control group ($P<0.001$) (Table 4).

Discussion

The results of the present study showed that resistance training along with melatonin supplementation significantly increased the levels of LH ($P=0.001$) and FSH ($P=0.001$) and significantly reduced the PGF2a level ($P=0.001$). Probably, the dysfunction of a hormone that is related to the hypothalamus (gonadotropin-releasing hormone) causes the inhibition of estrogen and subsequently a decrease in the release of hormones such as LH, FSH and disruption of ovulation and menstrual cycle in women [14]. From the hormonal point of view, the stress caused by aerobic exercise leads to the release of corticotropin and the suppression of gonadotropin, which subsequently leads to a decrease in progesterone and menstrual disorders [15]. However, in the present study, resistance training led to an increase in LH and FSH hormone levels. The reason can be the difference in the type and intensity of exercises and the metabolic response of women. Although reports confirm the positive effects of moderate-intensity exercise on dysmenorrhea symptoms [16], high-intensity and long-term exercises,

Table 1. Demographic characteristics of the participants

Factor	Group	Mean±SD
Age (y)	Training+melatonin	21.2±63.43
	Training+placebo	20.2±33.98
	Melatonin	21.3±24.07
	Control	20.2±76.89
Weight (kg)	Training+melatonin	61.3±21.48
	Training+placebo	59.4±99.37
	Melatonin	62.3±2.62
	Control	60.5±41.26
Height (m)	Training+melatonin	1.5±62.13
	Training+placebo	1.3±60.03
	Melatonin	1.3±63.49
	Control	1.3±62.71
BMI (kg/m²)	Training+melatonin	23.4±36.25
	Training+placebo	23.3±43.48
	Melatonin	23.2±40.84
	Control	23.4±5.8

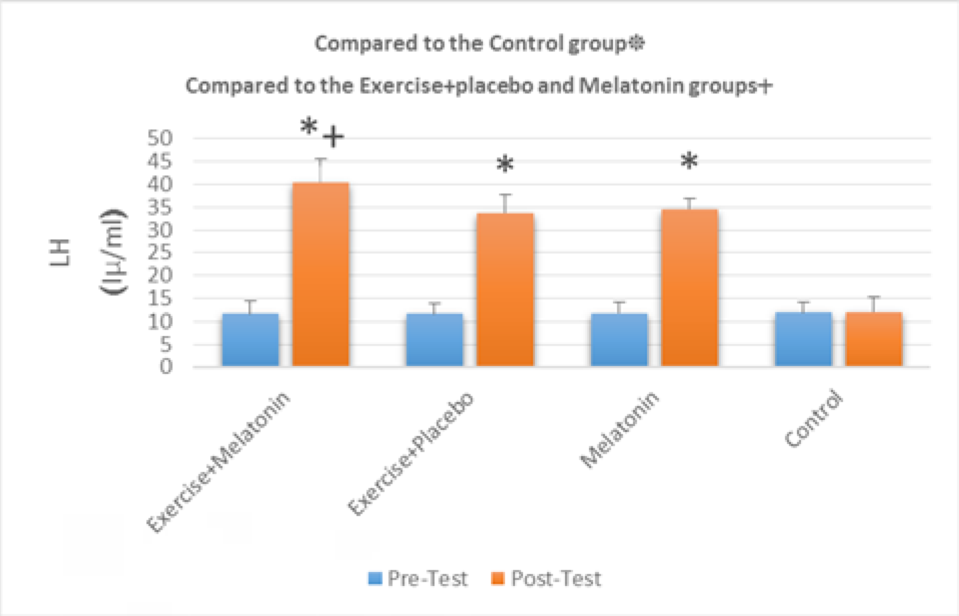

Figure 1. The LH concentration in the study groups

Table 2. Results of Bonferroni post hoc test for the LH level

Group		Mean Difference	Sig.
Training+melatonin	Training+placebo	3.327	0.012*
	Melatonin	2.906	0.036*
	Control	13.981	0.001*
Training+placebo	Melatonin	-0.420	1.000
	Control	10.654	0.001*
Melatonin	Control	11.075	0.001*

*Significant level <0.05.

including exercises to lose weight, can increase menstrual disorders in women with primary dysmenorrhea [17]. Therefore, the prescribed exercise protocol for these women can have a great impact on hormonal changes and the menstrual cycle.

Melatonin hormone receptors in the ovary and inside the follicular fluid play a role in regulating the secretion of sex steroids in different stages of maturation of the ovarian follicles. In addition, melatonin is a potent antioxidant and free radical scavenger that protects ovarian follicles during follicular maturation [18]. Serum melatonin increases in response to hunger and heavy exercise, which, if continued, causes cessation of menstruation. Melatonin also directly controls ovarian activity. The concentration and duration of melatonin production are abnormally high in women with hypothalamic menstrual cycle cessation. Women with this condition cannot ovulate because melatonin prevents the increase of hormones necessary for ovulation [19]. According to the results of a study, melatonin therapy significantly reduced the release of prostaglandins from the hypothalamus in rats. Melatonin modulates hypothalamic-pituitary activity at least by inhibiting hypothalamic prostaglandin synthesis. Prostaglandins cause uterine muscle contractions or muscle cramps. Melatonin prevents the production of prostaglandins in the uterus and hypothalamus [20]. Melatonin has also high anti-inflammatory effects. Part of these anti-inflammatory effects may be related to the reduction of prostaglandin production during the inflammatory process [3]. In a study, melatonin's effect on preventing prostaglandin production has been mentioned [21].

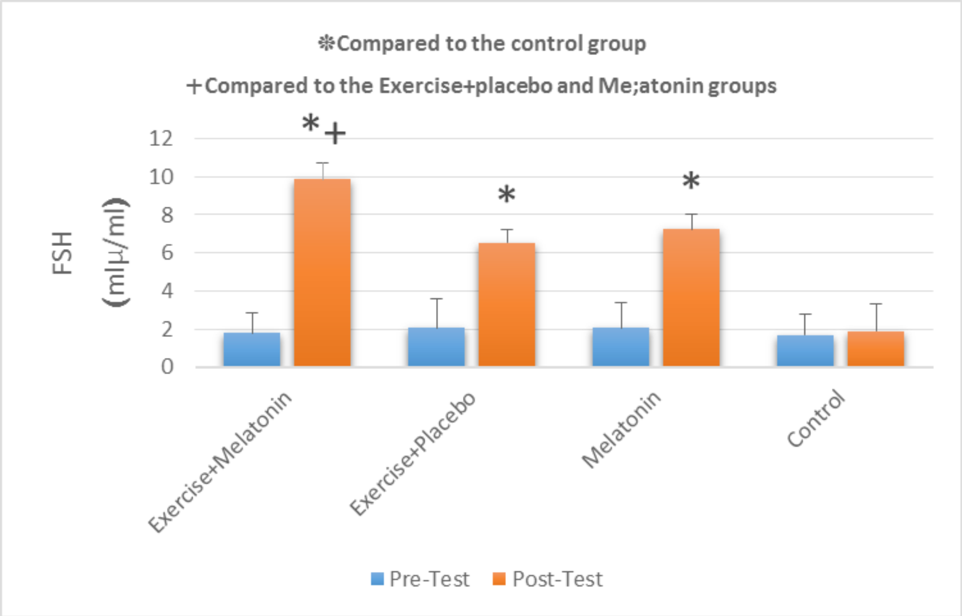

Figure 2. The FSH concentration in the study groups

Table 3. Results of Bonferroni post hoc test for the FSH level

Group		Mean Difference	Sig.
Training+melatonin	Training+placebo	1.524	0.003*
	Melatonin	1.171	0.031*
	Control	4.034	0.001*
Training+placebo	Melatonin	-0.353	1.000
	Control	2.510	0.001*
Melatonin	Control	2.863	0.001*

*Significant level <0.05.

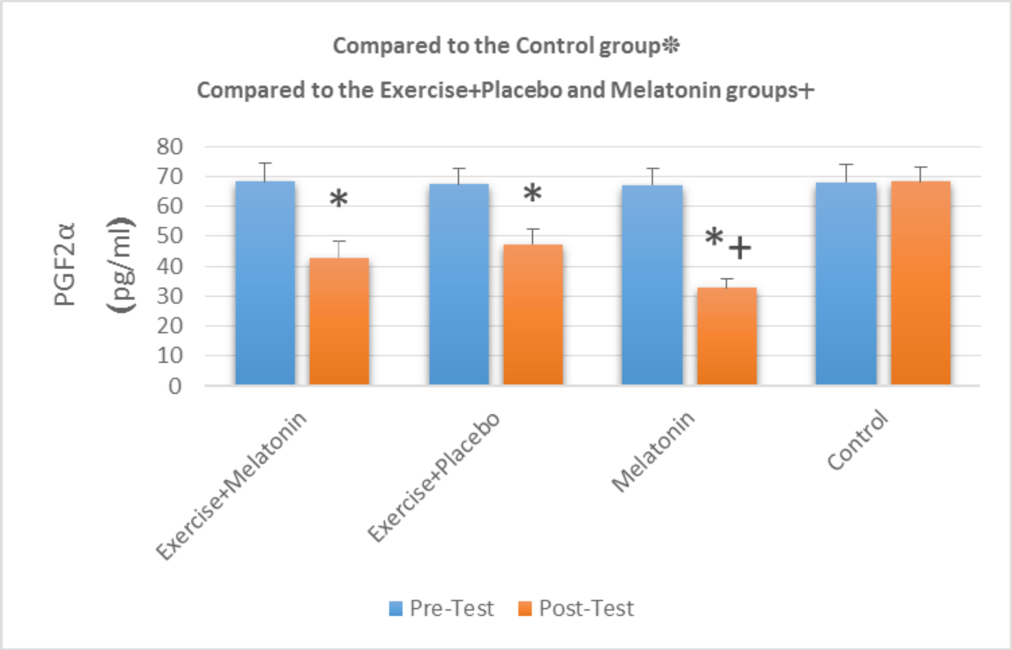

Figure 3. The PGF2α concentration in the study groups

Table 4. Results of Bonferroni post hoc test for the PGF2α level

Group		Mean Difference	Sig.
Training+melatonin	Training+placebo	-1.904	1.000
	Melatonin	5.568	0.030*
	Control	-12.663	0.001*
Training+placebo	Melatonin	7.472	0.002*
	Control	-10.759	0.001*
Melatonin	Control	-18.231	0.001*

*Significant level <0.05.

The duration of the menstrual cycle and the duration and amount of bleeding are significantly different in healthy women. The existence of significant deviations in these factors indicates the presence of functional or anatomical abnormalities. Menstrual disorders are classified based on the age of onset, frequency, duration and quantity of bleeding, and associated symptoms (e.g. pain). These disorders are more prevalent in adolescence than in older ages, because the physiological cycles of the hypothalamus, ovary, and uterus have not yet developed and various factors play a role in causing this disorder. The increase of prostaglandins in the endometrium after the decrease of progesterone at the end of the luteal phase leads to an increase in myometrial tone and hypercontraction of the uterus. A three-fold increase in endometrial prostaglandins occurs from the follicular to the luteal phase, and a further increase occurs during menstruation [22]. Therefore, the reduction of prostaglandin due to the use of melatonin is also a factor in increasing or adjusting the levels of LH and FSH.

Conclusion

The resistance training protocol used in this study is effective for women with primary dysmenorrhea. Melatonin, by affecting gonadotropin hormones as well as prostaglandin, overcomes the hormonal disorders caused by dysmenorrhea and can eliminate its symptoms.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Islamic Azad University, Neyshabur Branch (Code: IR.IAU.NEYSHABUR.REC.1401.008) and registered by the Iranian Registry of Clinical Trials (IRCT) (Code: IRCT20230703058653N1).

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Authors contribution's

Conceptualization and supervision: All Authors; Methodology and resources: Neda Kafi and Amene Barjaste Yazdi; Investigation and writing the original draft: Neda Kafi; Review and editing: Amene Barjaste Yazdi.

Conflict of interest

The authors declared no conflict of interest.

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