

## Antioxidant Capacity of Melatonin against Oxidative Stress Caused by Exercise-Induced Weight Loss in Rats

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### Abstract

Antioxidant supplements, such as melatonin, are employed to prevent oxidative stress during exercise. The objective of this study was to assess the antioxidant capacity of melatonin supplementation against oxidative stress induced by the weight loss observed during exercise. A cohort of forty male Wistar Albino rats was subjected to 10 days of jogging exercises. These rats were bifurcated into two groups based on the extent of weight loss incurred. Within each group, two subgroups were demarcated. Subsequently, Melatonin (5 mg/kg) was administered to each subgroup in each group. The other subgroups were designated as control subgroups. Blood samples were collected after 10 d. Superoxide dismutase (SOD), total antioxidant status (TAS), glutathione peroxidase, melatonin, and malondialdehyde levels were analyzed in blood samples. SOD, glutathione peroxidase, TAS, and melatonin levels in the melatonin subgroup were higher than those in the control subgroup in the non-weight loss group. In contrast, the malondialdehyde levels were lower. Melatonin levels in the melatonin subgroup were higher than those in the control subgroup in the weight loss group. Conversely, the SOD and TAS levels were lower. In addition, there was a positive correlation between weight loss and malondialdehyde levels and a negative correlation with SOD, TAS, and melatonin levels. Melatonin (5 mg/kg) supplementation showed antioxidant capacity in exercise without weight loss, but was insufficient in exercise with weight loss.

### Keywords

Antioxidant Capacity, Exercise, Melatonin, Oxidative Stress, Weight Loss.

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## INTRODUCTION

More than two-thirds (71.6%) of the adult population in the United States are overweight or obese (1). Additionally, obesity is a growing global health issue (2). Numerous strategies have been proposed to address this health problem (1). Exercise is one of these strategies and holds significant potential for improving the health status of obese individuals (3,4). However, the clinical efficacy of exercise for weight loss remains a subject of much controversy (5). Exercise may induce an increase in oxidative stress, contingent on its duration and intensity. In an exceptionally intense exercise regimen, the entire body consumes approximately 20 times more oxygen than during normal rest, and this rate can escalate up to 200 times in the muscles engaged in the exercise (6). Oxidative stress is characterized by the imbalanced production of reactive oxygen species and the antioxidant defense systems striving to balance this unbalanced production (7). While these two components of the oxidative stress-related spectrum are equilibrated during regular moderate exercise, they shift unfavorably towards the overproduction of reactive oxygen species during acute and vigorous exercise (8).

Melatonin exerts antioxidant effects by directly detoxifying reactive oxygen and reactive nitrogen species, and indirectly suppressing the activity of pro-oxidant

enzymes while stimulating antioxidant enzymes. Additionally, apart from these well-defined effects, melatonin has been reported to chelate metals involved in Fenton/Haber-Weiss reactions. Melatonin's distribution is uneven, with high concentrations found in mitochondria. Consequently, the intracellular distribution of melatonin aids its capacity to resist oxidative stress and cellular apoptosis (9).

Administering antioxidant supplements immediately before or during a workout session can diminish muscle damage and oxidative stress markers. Supplementation with melatonin protects skeletal muscles against damage induced by oxidative stress, while blueberries with a high concentration of melatonin reduce oxidation (10). Melatonin supplementation demonstrates favorable effects in modulating oxidative stress. The intake of melatonin supplements prior to maximal running exercise may protect the athlete from damage caused by oxidative stress (11).

This study aimed to investigate the effects of melatonin supplementation on exercise-induced oxidative stress. We also explored the impact of melatonin on oxidative stress associated with weight loss, which can be observed during exercise. Furthermore, our goal was to assess the relationship between the weight loss that can

be observed with exercise and antioxidant parameters.

## MATERIALS AND METHODS

### Groups and study design

The experimental animals were provided by the Aydin Adnan Menderes University Medical Faculty Experimental Animal Center. Forty male Wistar Albino rats, weighing 380-465 grams were included in the study. The rats were housed in transparent polyester cages and given standard rat chow along with tap water throughout the study period. There were no dietary restrictions during the study period. The cage was cleaned every two days. The rats were divided into two main groups, each having four subgroups. Group 1 consisted of rats without weight loss (n=20). This group was further divided into two subgroups: the 1C (Control) subgroup, which solely participated in exercised, and the 1M (Melatonin) subgroup, which received melatonin supplementation (5 mg/kg/day intraperitoneal) in addition to exercise (n=10). Group 2 comprised rats with weight loss (n=20). A niacin supplement (360 mg/kg/day oral gavage) was administered to this group because it aids in weight loss by increasing the nicotinamide adenine dinucleotide (NAD) content and energy consumption (12).

Similar to Group 1, Group 2 was divided into two subgroups: the 2C subgroup,

which exclusively participated in exercised, and the 2M subgroup, which received melatonin supplementation along with exercise (n=10).

### Procedures on rats

The Ethics Committee decision required for the study was obtained from the Animal Experiments Local Ethics Committee Center of Aydin Adnan Menderes University (decision number 6453101). Throughout the study, the protocols adhered to the principles outlined in the Declaration of Helsinki (1964) regarding the treatment of experimental animals. All animal procedures were conducted at the Aydin Adnan Menderes University Medical Faculty Experimental Animals Center. The exercise protocol utilized was based on the model established by Keskin et al. (13). In accordance with this model,

rats were subjected to treadmill exercise for 15 min each day over a span of 10 days, at a speed of 20 m/min (equivalent to 1.2 km/h) on a level surface. The exercise apparatus employed was the Dynamic 503 (China).

Niacin was obtained from Sigma-Aldrich (Missouri, USA) as a 100 g powder preparation. The solution dose was determined based on the study by Keskin (14). The niacin supplement (360 mg/kg/day) was administered orally, 30-45 minutes before exercise session.

Melatonin was procured from Sigma-Aldrich (Missouri, USA) in the form of a 1 g

powder preparation. The solution dose was established based on the study conducted by by Jitca et al. (8). Melatonin supplement (5 mg/kg/day) was administered intraperitoneally, 30-45 minutes before to the exercise session.

One day after the end of the 10-day exercise, approximately 7 mL of blood samples were collected intracardially under anesthesia with induced by ketamine and xylazine.

### **Biochemical processes**

All biochemical analyzes were conducted using a spectrophotometric method with a Biotek Epoch instrument (Canada). The method outlined in the study by Tastan et al. (15) was utilized as a reference for malondialdehyde analysis. Similarly, the methodology presented in the study by Sarikaya et al. (16) was employed as a reference for SOD analysis. The conversion of xanthine to uric acid is catalyzed by xanthine oxidase, which forms superoxide. When superoxides are formed, nitroblue-tetrazolium chloride forms formazan, a purple-colored compound. The color intensity was spectrophotometrically measured at a wavelength of 560 nm. The study by Bilgic et al. (17) was taken as reference for Glutathione peroxidase (GPX) analysis. The Rel Assay

TAS Analysis Kit (Turkey) was used for TAS analysis. The Elabscience Rat Melatonin Assay Kit (United States) was used for melatonin analysis.

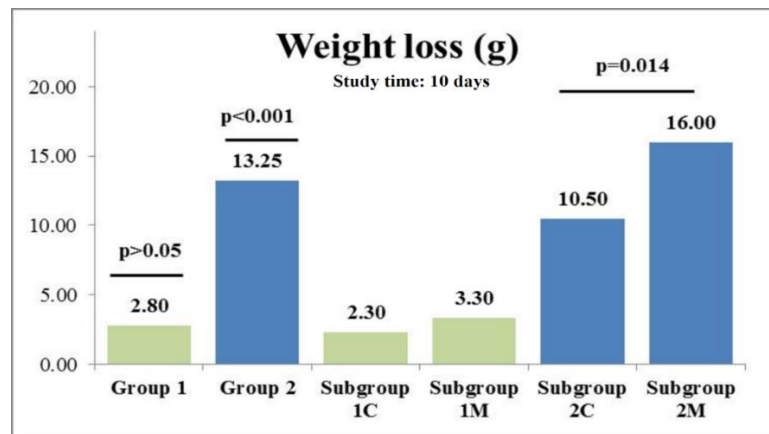
### **Statistical analysis**

Statistical Package for the Social Sciences IBM (NY, USA) for Windows 22.0 program was employed for statistical analysis. The data of the groups were compared using an independent sample t-test. Pearson's correlation analysis was performed to determine the correlation. Statistical significance was set at a threshold of 0.05.

## **RESULTS**

### **Changes observed in body weights of rats**

The rats' body weights were recorded daily during the entire study period. On the first day of the study, the means body weight of the rats in Group 1 was 427.05 g, while in Group 2, it was 404.10 g. On the final day of the study, the means body weight was 424.25 g in Group 1 and 390.85 g in Group 2. Notably, a significant weight loss was observed in Group 2 throughout the study, whereas Group 1 exhibited no significant weight change (Figure 1). Furthermore, within Group 2, subgroup 2M noticed a higher observed weight loss compared to subgroup 2C (Figure 1).



**Figure 1.** Weight loss observed in the groups

### Laboratory findings of the subgroups

The SOD ( $p=0.001$ ), TAS ( $p<0.001$ ), GPX ( $p<0.001$ ), and serum melatonin ( $p=0.002$ ) levels of subgroup 1M were found

to be higher than those of subgroup 1C. Moreover, malondialdehyde levels of subgroup 1M were found to be lower than those of subgroup 1C ( $p=0.003$ ) (Table 1).

**Table 1.** Subgroups within Group 1 Clarifies The Relationship Between The Subgroups and The Main Group

Parameters	Subgroup 1C X±SD	Subgroup 1M X±SD	p	Effect Size
MDA ( $\mu\text{mol/L}$ )	3.01±0.53	2.09±0.67	0.003	1.529
SOD (U/mL)	8.74±1.08	12.52±2.57	0.001	1.917
GPX (U/L)	526.00±99.54	1029.92±249.34	<0.001	2.654
TAS ( $\mu\text{mol Trolox Equiv./L}$ )	797.61±44.2	1205.32±38.84	<0.001	9.800
Melatonin (pg/ml)	135.72±26.81	189.09±39.85	0.002	1.571

Abbreviations: Malondialdehyde (MDA), Superoxide dismutase (SOD), Glutathione peroxidase (GPX), Total antioxidant status (TAS).

Serum melatonin levels of subgroup 2M were found to be higher than those of subgroup 2C ( $p=0.002$ ). Moreover, SOD

( $p<0.001$ ) and TAS ( $p=0.017$ ) levels of subgroup 2M were found to be lower than those of subgroup 2C (Table 2).

**Table 2.** Subgroups within Group 2 Clarifies The Relationship Between The Subgroups and The Main Group

Parameters	Subgroup 2C X±SD	Subgroup 2M X±SD	p	Effect Size
MDA ( $\mu\text{mol/L}$ )	3.23±0.50	3.77±0.54	>0.05	-
SOD (U/mL)	8.37±1.01	6.01±0.61	<0.001	2.831
GPX (U/L)	1033.44±198.05	1152.33±313.19	>0.05	-
TAS ( $\mu\text{mol Trolox Equiv./L}$ )	1188.83±54.27	1113.56±72.11	0.017	1.179
Melatonin (pg/ml)	142.80±24.80	189.71±31.48	0.002	1.655

Abbreviations: Malondialdehyde (MDA), Superoxide dismutase (SOD), Glutathione peroxidase (GPX), Total antioxidant status (TAS).

In Group 1, where weight loss was not significant, melatonin supplementation led to increased SOD, GPX, TAS, and serum melatonin levels, accompanied by a decreased in malondialdehyde levels. Conversely, in Group 2, where weight loss was significant, melatonin supplementation, was associated with increased serum melatonin levels and weight loss, along with decreased SOD and TAS levels.

### Correlation analysis

Correlation analysis was performed to determine the relationship between weight

loss and malondialdehyde, SOD, GPX, TAS and serum melatonin levels. The malondialdehyde, SOD, GPX, and TAS levels in Group 2 where weight loss was significant were evaluated using correlation analysis. The serum melatonin levels in subgroup 2C were evaluated using correlation analysis between serum melatonin levels and weight loss.

A positive correlation was found between malondialdehyde levels and weight loss. A negative correlation was found between weight loss and SOD, TAS, and serum melatonin levels (Table 3).

**Table 3.** Results of Correlation Analysis between Analyzed Parameters and Weight Loss

Parameters	Correlation coefficient	P
MDA	0.853	<0.001
SOD	-0.970	<0.001
GPX	-0.286	>0.05
TAS	-0.878	<0.001
Melatonin	-0.956	<0.001

Abbreviations: Malondialdehyde (MDA), Superoxide dismutase (SOD), Glutathione peroxidase (GPX), Total antioxidant status (TAS).

## DISCUSSION

Obesity increases the risk of various health problems, including diabetes, arthritis, high blood pressure, cancer, stroke, and heart attack. Weight loss can reduce these risk factor. A healthy way to lose weight is to eat fewer calories and exercise regularly (18). While the benefits of exercise for weight loss are in the foreground, the potential harm arising from heightened oxidative stress due to the exercise's duration and intensity should not be disregarded. Although this harm is not

observed in short-term low-intensity exercises, they occur in acute, long-term, and high-intensity exercises (19).

Antioxidant supplements are extensively used to mitigate the oxidative stress induced by exercise. Melatonin,  $\alpha$ -lipoic acid, and vitamin E have shown promise in reducing markers of exercise-induced oxidative stress. However, evidence regarding their effects on endurance performance is either limited or inconclusive (20). Borges et al. concluded that SOD activity increased by 22% with 20



mg/dL melatonin supplementation, subsequently reducing exercise-induced muscle oxidative stress and inflammation (21). Another study demonstrated that melatonin supplementation of 25 mg/kg increased antioxidant activity while decreased tissue malondialdehyde and 3-nitrotyrosine levels (22). Involving human participants, another study concluded that oral melatonin supplementation of 15 mg during high-intensity exercise effectively decreased oxidative stress levels, leading to significant increases in antioxidant enzyme activities and lowered lipid peroxidation levels (23).

In this study, rats were exercised for 10 days. Melatonin (5 mg/kg) was administered daily prior to exercise. In the non-weight loss group, the subgroup receiving melatonin supplementation exhibited higher SOD activity, GPX activity, TAS levels, and serum melatonin levels compared to the control subgroup. Conversely, malondialdehyde levels were found to be lower in the melatonin-supplemented group.

In the weight loss group, the serum melatonin levels in the subgroup that administered melatonin supplementation were higher compared to the control subgroup. However, SOD and TAS levels were lower. On the other hand, the weight loss observed in the melatonin-supplemented subgroup was higher than in the control subgroup. In addition, the weight loss

exhibited in this study indicated a strong negative correlation between SOD activity, TAS levels, and serum melatonin levels, along with a notable positive correlation between malondialdehyde levels.

Numerous studies have explored the combination of melatonin with exercise. A study involving rats subjected to a 16-week, melatonin regimen highlighted the significant role of melatonin supplementation in facilitating the necessary metabolic adaptations prompted by aerobic exercise (24). Pobocik et al. reached the conclusion that moderate aerobic exercise could elevate melatonin production (25).

In this study, although the serum melatonin levels were negatively correlated with weight loss, serum melatonin levels in the melatonin-supplemented subgroup of the weight loss group were higher than those in the control subgroup. However, the weight loss observed within the melatonin-supplemented subgroup of the weight loss group exceeds that of the control subgroup.

In a study on body weight with melatonin supplementation, obese rats were administered 30 mg/kg melatonin supplementation for three weeks. Another study reported that melatonin supplementation halved body weight gain and improved feed efficiency (26). In another study of obese people, it was concluded that 3 mg/day melatonin supplementation did not significantly reduce weight and body mass

index, but reduced body fat mass percentage (27). A recent study shows that melatonin acts as a buffer for changes in body weight (28). In this study, a significantly higher level of weight loss was found in the melatonin supplement subgroup of the weight loss group than in the control subgroup.

In this study, only glutathione peroxidase did not show any correlation among the parameters analyzed for weight loss. This absence of correlation was attributed to the niacin supplementation administered to the weight loss group. Niacin serve as a precursor to nicotinamide adenine dinucleotide phosphate, a cofactor required by the glutathione reductase enzyme within the glutathione redox cycle. Both glutathione peroxidase and glutathione reductase contribute to this cycle (29). In addition, when comparing the parameters of the subgroups of the weight loss group, no significant decrease was found in the glutathione peroxidase activity of the melatonin supplemented subgroup compared to that of the control subgroup. However, a significant decrease was observed in SOD and TAS levels in this subgroup.

In a study focused on weight loss among obese children, significant reductions were observed in body mass index, waist-to-hip ratio and fat mass among the obese children compared to the control group. Conversely, malondialdehyde levels increased. Malondialdehyde were correlated with waist-

to-hip ratio, body mass index, and fat mass, and the oxidant status returned to normal after six months of dietary restriction (30). In this study, which lasted for 10 days, malondialdehyde was found to be correlated with weight loss. However, no significant difference was found in the comparison of malondialdehyde levels between the subgroups of the weight loss group. In addition, the melatonin-supplemented subgroup of the weight loss group showed a higher level of weight loss than the control subgroup. There was no significant difference in malondialdehyde levels due to the antioxidant effect of melatonin supplementation. SOD and TAS levels decreased in this subgroup despite melatonin supplementation. This suggests that SOD and TAS levels are engaged in counteracting the elevated oxidative state attributed to y malondialdehyde levels.

Although there are numerous studies on the effect of melatonin supplementation on the prevention of exercise-induced oxidative stress, there is no consensus on this effect. These numerous studies are sufficient to indicate that melatonin ingestion is effective against oxidative stress, but are not sufficient to indicate recommendations for its safe dose. Clinical studies are required to determine the optimal melatonin (31). In this study, we determined that a melatonin supplementation 5 mg/kg effectively countered exercise-induced oxidative



stress when exercise did not lead to significant weight loss in rats. However, this dosage proved insufficient in scenarios where exercise induced substantial weight loss.

Previous studies have not reached a consensus regarding the antioxidant properties of varied melatonin supplementation dosages. Hence, this study aimed to investigate the antioxidant effects of melatonin supplementation by forming two distinct groups, one with weight loss and one without.

The study findings indicate that a melatonin supplementation of 5 mg/kg exhibited a significant antioxidant effect in exercises without inducing weight loss. However, this effect did not hold significant in exercises involving weight loss. These outcomes suggest a potential association between melatonin supplementation's antioxidant properties and weight loss.

Essentially, it implies that the antioxidant impact of melatonin supplementation may be inadequate in the face of heightened oxidative stress due to weight loss induced by exercise. Nevertheless, more extensive research is warranted, considering that this study solely examined a melatonin supplementation dosage of 5 mg/kg. A more precise understanding can potentially be

gleaned from investigations into various dosages and diverse populations groups.

No financial support was received for this study. The limitations of this study was that it was performed using a single dose. However, it can be a reference for similar studies to be performed with different doses in the future.

## CONCLUSIONS

This study concludes that melatonin supplementation was sufficient to combat exercise-induced oxidative stress when no significant weight loss was observed. However, melatonin supplementation was not sufficient to combat exercise-induced oxidative stress, when a significant weight loss was observed during exercise. This discrepancy may be attributed to the weight loss itself. Additionally, it was observed that melatonin supplementation resulted in increased weight loss, particularly in scenarios involving substantial weight loss during exercise.

In addition, weight loss was positively correlated with malondialdehyde and negatively correlated with SOD, TAS and serum melatonin levels. Considering the circumstances of significant weight loss was during exercise, higher dosage of melatonin supplementation might offer effective assistance.

## AUTHOR CONTRIBUTIONS

All authors contributed equally to this study (conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis, wrote the paper).

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Not applicable.

## CONFLICT OF INTEREST

There are no conflicts of interest.

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