


# The Effect of Daytime Ingestion of Melatonin on Thyroid Hormones Responses to Acute Submaximal Exercise in Healthy Active Males: A Pilot Study

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## Abstract

It is well known that exercise increases the activity of thyroid glands and raises the blood level of melatonin. The increase of melatonin during exercise may be linked to a rise in thyroid-stimulating hormone (TSH). No previous study has investigated the combined effects of melatonin ingestion and acute submaximal exercise on thyroid hormones' responses. The purpose of this pilot study was to explore the effects of daytime ingestion of melatonin on thyroid hormones' responses to acute submaximal exercise. After 50 min of either melatonin (6 mg) or placebo ingestion, eight physical education students (mean  $\pm$  standard deviation of age:  $22 \pm 1$  years) were asked to run for 45 min at 60% of their maximum aerobic speed. Free thyroxine (fT4) and TSH were measured in plasma samples before and immediately after exercise. After submaximal exercise, TSH increased by 54% in both placebo and melatonin conditions. There was no significant (Condition  $\times$  Exercise) interaction, and no significant condition effect for TSH. The fT4 remained unchanged before/after submaximal exercise in both placebo [15.2 (1.9) and 15.0 (1.6) pmol/L, respectively,  $p > .05$ ], and melatonin [16.7 (2.7) and 16.3 (2.7) pmol/L, respectively,  $p > .05$ ] conditions. There was no significant (Condition  $\times$  Exercise) interaction, no significant exercise effect, and no significant condition effect for fT4. To conclude, acute melatonin ingestion did not affect thyroid hormones' responses to submaximal exercise.

## Keywords

biological rhythm, inflammation, metabolism, oxidative stress, thyrotropic axis

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## Introduction

It is well known that glands activity and hormones production (i.e., cortisol and thyroid hormones) are affected by physical activity (Deligiannis et al., 1993; Dergaa, Ben Saad, et al., 2021; Souissi et al., 2021). The thyroid is one of the most affected glands by the submaximal exercise (Deligiannis et al., 1993; Gagnon et al., 2014; Hackney & Saeidi, 2019). Triiodothyronine (T3) and thyroxine (T4) are both produced by the thyroid gland and can be detected in the free forms (i.e., fT3, fT4—free thyroxine). Thyroid hormones are widely known for their role in thermoregulation and fatty acid oxidation (Gullu et al., 2004). Thyrotropin-releasing hormone is produced by the hypothalamus, which stimulates the pituitary gland to generate

thyroid-stimulating hormone (TSH; Gullu et al., 2004). The adenohypophysis produces TSH, which stimulates the production of thyroid hormones (i.e., T3 and T4).

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Therefore, TSH is a thyroid function marker (Kosack et al., 2012). TSH influences fat synthesis, mobilization, and breakdown, as well as the amount of catecholamine receptors on cell surfaces, which influences heart rate (Mullur et al., 2014; Souissi et al., 2021). In trained athletes, increased activity of the thyroid hormones, as well as the adrenal cortex, plays a major role in adaptations to physical exercise (Deligiannis et al., 1993). Submaximal exercise results in elevated blood TSH levels (Ciloglu et al., 2005). It has been reported that TSH secretion possibly increases both during and hours after prolonged submaximal exercise to increase metabolism (Canali & Krueel, 2001; Ciloglu et al., 2005; Pardini, 2001).

Interestingly, the increase of TSH after exercise may be associated with an increase in melatonin secretion (Escames et al., 2012; Van Reeth et al., 1994). However, the relation between melatonin, exercise, and TSH in the morning is not yet well established. Melatonin (*N*-acetyl-5-methoxytryptamine), which is the pineal gland's primary product, regulates circadian rhythm, sleep, and sexual behavior (Dergaa, Varma, et al., 2021; Pandi-Perumal et al., 2008; Souissi et al., 2019). Melatonin is known to have antioxidant and anti-inflammatory effects (Escames et al., 2012; Kruk et al., 2021; Souissi et al., 2018, 2019; Watson et al., 2016). Several researchers have looked into the effects of melatonin on endurance exercise (Alonso et al., 2006; Maldonado et al., 2012; Souissi et al., 2018, 2019; Veneroso et al., 2009). A single dose of exogenous melatonin, given before submaximal exercise, was reported to reduce oxidative stress, inflammation, and muscle damage (Alonso et al., 2006; Kruk et al., 2021; Maldonado et al., 2012; Veneroso et al., 2009).

To resume, because physical exercise increases the activity of thyroid glands (Deligiannis et al., 1993; Dergaa, Ben Saad, et al., 2021; Souissi et al., 2021) and rises the blood level of melatonin (Escames et al., 2012), the increase of melatonin during exercise may be linked to a rise in TSH. However, to the best of the authors' knowledge, no previous study has investigated the acute combined effects of daytime melatonin ingestion and exercise on humans' thyroid hormones' responses. The present pilot study examined the possible effects of daytime acute ingestion of melatonin on fT4 and TSH responses to submaximal exercise. We hypothesized that melatonin ingestion may favor the rise of TSH during exercise.

## Population and Methods

### Participants

Only healthy physical education male students participated in this study. Participants were physically active

and had normal corpulence status (body mass index: 18.5–24.9 kg/m<sup>2</sup>). The choice of student is argued by our tendency to focus on population who trained moderately. Participants were asked to refrain from exercise, alcohol, and caffeine-containing drinks for at least 24 hr before the measurements started. A cardiologist checked participants' medical history and reported that all participants were healthy and nonsmokers. The absence of any participant during the second/third sessions of the protocol was applied as an exclusion criterion. Participants were classified as neither morning nor evening type according to the Horne and Ostberg (1976) questionnaire. Participants have signed an informed consent, after receiving a complete verbal description of the protocol. The study protocol was in accordance with the Helsinki Declaration for conducting human experimentation and was approved by the Farhat HACHED ethical committee, Sousse, Tunisia (FH/1609021).

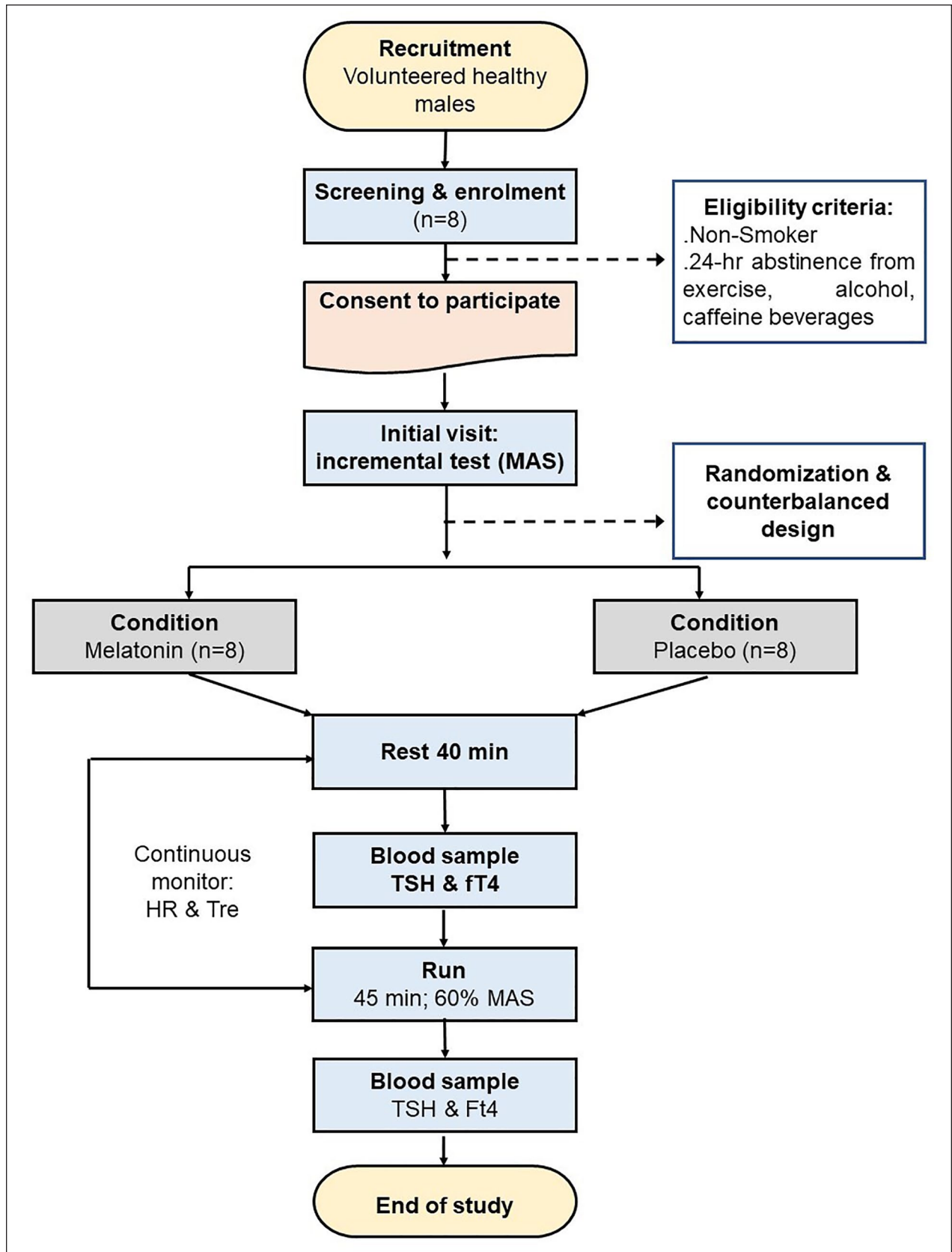
At 09:50 of the preliminary visit, an incremental test to exhaustion was used to determine maximum aerobic speed (MAS; Hagin et al., 2015). The experimental conditions (placebo or melatonin) were randomized and counterbalanced. The intervals between conditions were at least equal to 24 hr. Exercise is performed at 23°C ± 0.1°C (60% ± 3% humidity). All conditions were performed indoors at the same time of the day (i.e., between 8:00 and 10:35) to minimize the effects of diurnal variations in the aerobic and anaerobic contributions to physical performance (Dergaa, Varma, et al., 2021; Souissi et al., 2020). Figure 1 illustrates the study design.

### Sample Size

The sample size was calculated according to the following formula (Kang et al., 2008):  $N = Z\alpha^2 s^2/d^2$ , where “*s*” is the standard deviation ( $SD = 0.415 \mu\text{IU/mL}$ ) and “*d*” is the accuracy of estimate or how close it is to the true mean ( $M = 0.29 \mu\text{IU/mL}$ ). Given the pioneer character of our study, the “*s*” was collected from the study of Deligiannis et al. (1993), including 15 athletes who swam front crawl for 30 min at a moderate speed. At 20°C, their TSH increased by 90.4%, from  $1.15 \pm 0.42 \mu\text{IU/mL}$  (pre-exercise) to  $2.19 \pm 0.41 \mu\text{IU/mL}$  (post-exercise). “*Z*α” is the normal deviate for a one-tailed alternative hypothesis at a level of significance (*Z*α is equal to 1.64 at an error rate of 0.05%). The appraised sample size gives a sample of six participants. The assumption of 30% of nonattendance during the conditions gives a revised sample of eight participants [= 5.5/(1 – 0.30)].

### Experimental Protocol

From 08:20 to 09:00, participants rested in a seated position. At 09:00, the participant ingested whether the 6 mg of



**Figure 1.** Flowchart of the Study's Methodology

Note. MAS = maximum aerobic speed; HR = heart rate; Tre = rectal temperature; TSH = thyroid-stimulating hormone; ft4 = free thyroxine.

**Table 1.** Characteristics of Participants (N = 8).

Data	Mean $\pm$ SD
Age (years)	22 $\pm$ 1
Height (cm)	178 $\pm$ 2
Weight (kg)	67.1 $\pm$ 2.8
Body fat (%)	20.7 $\pm$ 2.1
Muscle mass (%)	47.1 $\pm$ 1.5
Bone mass (kg)	9.3 $\pm$ 0.3

Note. Data were mean  $\pm$  standard deviation.

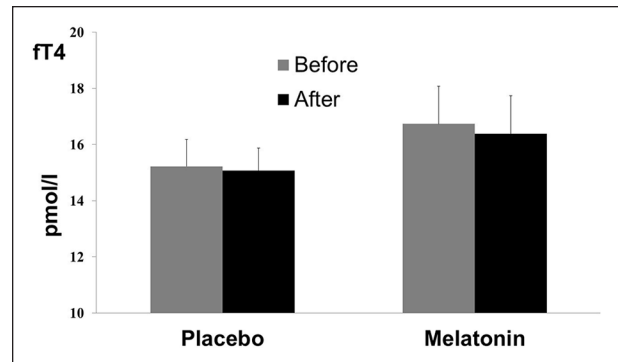
quick-release vegetable melatonin (Jamieson Laboratories, Canada) or placebo capsule with 500 mL of water before resting for 50 min (Figure 1). A heart rate monitor (Polar RS800, Polar Electro, FIN-90440 KEMPELE, Finland) and a rectal probe (Universal YSI400 Adults, China) were used to continually record the heart rate and rectal temperature, respectively. Heart rate was expressed as a percentage of the predicted maximal heart rate ( $= 220 - \text{age (year)}$ ) (Robergs & Landwehr, 2002). Blood samples were collected at 09:40 (before exercise). The treadmill (Finnlo by HAMMER, Germany) workout began at 09:50. Participants ran at 60% of their MAS for 45 min. Then, blood samples were recollected (after exercise) for measuring TSH and ft4 levels using immune-electrochemiluminescence on an automated Cobas e411 machine (Roche Diagnostics, USA).

### Statistical Analyses

All the statistical analyses were performed using Statistical Software, Version 10.0, for Windows (StatSoft, Maisons-Alfort, France). The results were presented as the mean  $\pm$  standard deviation throughout the text. The data were compared using repeated-measures analysis of variance. When necessary, the Bonferroni post hoc was applied to identify significant differences. Effect sizes were calculated as partial eta-squared  $\eta$  ( $\eta_p^2$ ). The level of significance was predetermined to be  $p < .05$  for all statistical analyses.

### Results

Eight healthy physical education students were included. Table 1 illustrates their anthropometric parameters. All the participants undergoing submaximal exercise successfully completed the exercise. Rectal temperature exceeds 38°C in both conditions. Heart rate increased progressively in both conditions without reaching the predicted maximal heart rate. In placebo condition, the heart rate increased from 74% of predicted maximal heart rate (at 5 min of exercise) to 85% of predicted maximal heart rate (at the end of the exercise). In melatonin condition, the heart rate



**Figure 2.** Free Thyroxine (ft4) Measures (Mean  $\pm$  Standard Deviation) Before and After Acute Submaximal Exercise of 45 Min in Placebo and Melatonin Conditions

increased from 73% of predicted maximal heart rate (at 5 min of exercise) to 83% of predicted maximal heart rate (at the end of the exercise). Participants seem to be under the same physiological stress in both conditions during the exercise.

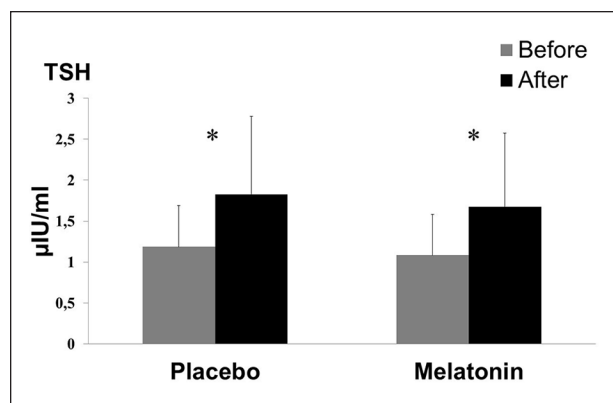
ft4 was stable before/after submaximal exercise in both placebo [15.2 (1.9) and 15.0 (1.6) pmol/L, respectively,  $p > .05$ ] and melatonin [16.7 (2.7) and 16.3 (2.7) pmol/L, respectively,  $p > .05$ ] conditions (Figure 2). There was no significant (Condition  $\times$  Exercise) interaction,  $F(1, 7) = 0.26, p = .62, (\eta_p^2) = 0.03$ ; no significant exercise effect,  $F(1, 7) = 0.79, p = .40, (\eta_p^2) = 0.10$ ; and no significant condition effect,  $F(1, 7) = 1.81, p = .21, (\eta_p^2) = 0.20$ .

TSH was increased after submaximal exercise in both placebo [by 54%: from 1.18 (0.99) to 1.82 (1.90)  $\mu\text{IU/mL}$ ,  $p < .001$ ] and melatonin [by 54%: from 1.08 (0.99) to 1.67 (1.83)  $\mu\text{IU/mL}$ ,  $p < .001$ ] conditions (Figure 3). There was no significant (Condition  $\times$  Exercise) interaction,  $F(1, 7) = 0.25, p = .63, (\eta_p^2) = 0.03$ , and no significant condition effect,  $F(1, 7) = 1.27, p = .29, (\eta_p^2) = 0.15$ .

### Discussion

To the finest of the authors' knowledge, this is the first investigation that evaluated the effects of daytime ingestion of melatonin on thyroid hormones' responses to acute submaximal exercise in healthy active males. The main result of the present study was that daytime melatonin ingestion did not affect thyroid hormones' responses to acute submaximal exercise.

In conditions with two levels (i.e., placebo and melatonin), TSH increased by 54% after submaximal exercise ( $p < .001$ ). This finding is in line with the one of Deligiannis et al. (1993), who reported that swimming for 30 min at 20°C boosted TSH levels considerably. Furthermore,



**Figure 3.** Thyroid-Stimulating Hormone (TSH) Measures (Mean  $\pm$  Standard Deviation) Before and After Acute Submaximal Exercise of 45 Min in Placebo and Melatonin Conditions

\*Significant difference compared with rest ( $p < .001$ ).

Deligiannis et al. (1993) identified that TSH increased by 90.4% after swimming at 20°C, remained unchanged at 26°C, and then declined at 32°C (Deligiannis et al., 1993). In fact, it has been reported that when exposed to cold, metabolic rates increase, whereas when exposed to heat and/or during exercise-induced hyperthermia (Febbraio et al., 1996; Souissi et al., 2019, 2021), metabolic rates drop (Dempsey & Astwood, 1943; Febbraio, 2001; Febbraio et al., 1996). Thyroid hormones stimulate sympathetic nerves that innervate brown adipose tissue to produce metabolic heat and act on skeletal muscle to produce heat (Cannon & Nedergaard, 2010). Thyroid hormones can act as a barrier to effective heat dissipation in hyperthermia conditions (Bowen et al., 1984; McMurray & Hackney, 2000). Therefore, the decrease in fT4 during submaximal exercise-induced hyperthermia by muscle working (Souissi et al., 2021) could be interpreted as an adaptive mechanism to hyperthermia. However, our finding indicated that fT4 did not show a significant decrease after submaximal exercise. Indeed, it is still unknown whether a longer duration of exercise or a hot condition than the ones used in our investigation would have decreased significantly plasma fT4. We highlight that thyroid function depends according to the exercise intensity, thermoregulatory control, and perhaps to other factors such as specific characteristics of the participants (Ciloglu et al., 2005; Deligiannis et al., 1993).

Given the pioneer character of our study, which aims to explore the impacts of acute daytime ingestion of melatonin on TSH and fT4 responses to submaximal exercise, a part of the discussion will concern the chronic effects of melatonin ingestion. The literature reported evidence for a net beneficial effect of chronic melatonin administration (El-Gendy et al., 2018; Potes et al., 2019). The latter is

reported to decrease pituitary levels and increase plasma levels of TSH in animals (Gordon et al., 1980; Panda & Turner, 1968). Animal studies have also demonstrated that melatonin interacts with other hormones to alleviate heat stress possibly with T4 and successfully modifies the adrenal function to relieve thermal stress (Sejian & Srivastava, 2010). Contrary to chronic melatonin ingestion, the results of the present study indicated that acute melatonin ingestion has no effect on plasma TSH levels. Therefore, it would be interesting to investigate in the future the effects of chronic melatonin ingestion on plasma TSH response to submaximal exercise.

### Study Limitations

Although our study has direct practical implications, because it is the first one coupling the effects of melatonin and submaximal exercise on thyroid hormones' secretion, its major limitation was that end-exercise values of melatonin, TSH, and fT4 were not corrected for plasma volume changes (Alis et al., 2015). In addition, it was better to analyze thyroid hormones, before and after (e.g., 30 or 60 min after the end of the exercise) the physical exercise, not only at the end of the exercise, as done in our study.

To conclude, the daytime ingestion of melatonin before 50 min of acute submaximal exercise did not favor the increase in TSH in response to exercise.

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### Declaration of Conflicting Interests

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