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Effects of Improved Sleep Quality with Administration of Melatonin plus GABA on Total-body Skeletal Muscle Mass of Amateur CrossFit Athletes

Fellipe Pinheiro Savioli *
Irmandade da Santa Casa de Sao Paulo, Brazil.

Jan Willem Cerf Sprey
Irmandade da Santa Casa de São Paulo, Brazil.

Paulo Afonso Mei
Department of Neurology and Sleep Medicine Sao Leopoldo Mandic Medical College, Campinas, Brazil.

Nicole Nardy Paula Razuck
Irmandade da Santa Casa de Sao Paulo, Brazil.

Gabriela Thabata Bruno Cilla
Cilla nutrition center, Brazil.

Tatiana Ciocler Trahtenberg
Santa Marcelina Medical College, Brazil.

Guilherme de Vieira Giorelli
Hospital Israelita Albert Einstein, Brazil.

Pedro Baches Jorge
Irmandade da Santa Casa de Sao Paulo, Brazil.

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Abstract

Purpose: Sleep and exercise influence each other through complex interactions. Sleep disorders incidence in athletes are high among several sports. **Method:** 24 CrossFit practitioners, of both genders, between the ages of 25 and 35, presenting difficulty in initiating sleep, with a total sleep time of less than 6 hours per night, were recruited into a double-blind, randomized, placebo-controlled trial that lasted 8 weeks. Participants received capsules containing 3 mg of melatonin + 1200 mg of GABA (gamma-Aminobutyric acid) or placebo at 10:00 pm daily. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), cortisol and

Author's e-mail: fellipesavioli@gmail.com **(Corresponding Author)**; jancerf@gmail.com; drkult@gmail.com; nnardy@gmail.com; ga.tbcilla@gmail.com; taticiocler@gmail.com; guilherme@giorelli.com.br; pbj@clinicasou.com.br.

testosterone levels were measured and total-body skeletal muscle mass (TBSMM) by Lee's equation performed by two different examiners. **Results:** Group melatonin + GABA gained an average of 600g of TBSMM while the control group lost 200g ($p = 0.295$). Both groups improve PSQI score ($p = 0.007$). No difference was found in cortisol and testosterone level. **Conclusions:** Although there was a difference between groups about TBSMM, it wasn't statistically significant. Further studies will be necessary to demonstrate evidence of increased TBSMM from better sleep quality, with a larger number of participants and a longer trial.
Keywords: CrossFit, exercise recovery, sleep quality, skeletal muscle mass.

INTRODUCTION

Nearly one third of the general population complains of insomnia (Ohayon 2011, Stewart et al 2006). Amateur and/or professional athletes have a higher incidence; Tuomilehto et al (2017) observed that 22% of professional ice hockey athletes had sleep issues during their holidays; however, during the championship season, that number rose to 46%. Swinbourne et al (2016) found that 50% of professional rugby and cricket athletes had sleep disorders, while Silvia et al (2016) reported that 77.6% of athletes in Olympic gymnastics have poor sleep quality. Erlacher et al (2011) observed that 65.8% of German athletes of different modalities had sleeping issues.

Some studies have suggested that the general population's average sleep duration has declined over the last few decades. Working conditions, associated with excessive screen use (cell phones, tablets, and computers) at night, have contributed to this situation (Christensen et al 2016; Rafique et al 2016).

Sleep disorders are a group of conditions composed of insomnia, sleep-related respiratory events (obstructive apnea, sleep-related hypoventilation), hypersomnolence, changes in the sleep-wake circadian cycle, parasomnias (somnambulism, night terror, confusional awakening), sleep-related movement disorders (restless legs syndrome, bruxism), among others (Neves et al 2017). Insomnia is considered the most common sleep disorder in the general population (6-10%) (Krystal & Sorscher 2016) and is clinically defined as "dissatisfaction with quality or quantity of sleep associated with a nocturnal symptom (difficulty initiating sleep and/or maintaining sleep or early awakening from sleep), causing impairment in daytime activities in physical (drowsiness, fatigue), mental (attention, concentration, behavioral and memory

changes), or social (family or work) spheres." The diagnostic criteria comprises three episodes per week for three months that cannot be better explained by another sleep disorder (Neves et al 2017).

Insomnia is a clinical diagnosis (Shelgikar & Chervin 2013). A polysomnography study is not routinely recommended, except when there is the possibility of another associated sleep disorder (Neves et al 2017). Medications, psychotherapy, and the combination thereof have been shown to help people with insomnia. Cognitive Behavioral Therapy (stimulus control, relaxation training, paradoxical intention, biofeedback, sleep hygiene) is a safe and effective way to treat insomnia by correcting inappropriate attitudes and beliefs about sleep, as well as disorders related to anxiety. Medication involves three different classes of drugs: those acting in the GABAergic system, those acting in the melatonergic system, and orexin receptor antagonists. Other "off-label" medications can also be prescribed, such as GABA-A receptor agonists, antidepressants, atypical antipsychotics, antiepileptics, melatonin, and antihistamines (Frase et al 2018).

Sleep disorders are directly related to metabolic changes, which may cause higher incidences of some chronic conditions, such as hypertension (Van Ryswyk et al 2018), type 2 diabetes mellitus (Larcher et al 2015), depression (Fang et al 2019), obesity (Reutrakul & Van Cauter 2018), and cancer (Yilmaz 2020; Lin et al 2019). They are also associated with mood changes (El-Ad & Lavie 2005; Triantafillou et al 2019), hormonal disorders (Wright et al 2015; Chopra et al 2017; Song et al 2015; Ilias et al 2002; Redwine et al 2000; Brandenberger et al 2000; Arnal et al 2016), and changes in the immune system (Irwin & Opp 2017; Ibarra-Coronado et al 2015; Besedovsky et al 2019).

A sleep restriction period promotes a catabolic hormonal environment where improving muscle mass or even maintaining it becomes more difficult. Among these changes, the most relevant are related to changes in cortisol, testosterone, and growth hormone (GH).

Cortisol production is controlled by the circadian rhythm (Abe et al 1979), with peak production in the morning a few minutes after waking and then a gradual decline throughout the day, reaching very low levels around midnight, followed by oscillations during sleep (Krieger et al 1971; Weitzman et al 1971). Due to cortisol's secretion pattern, measuring its levels can be a challenge, though important differences can

be seen when measurements are taken at the same period of the day (e.g.: morning measurements at 8 am and 10 am). The same person may have different levels of cortisol secretion during the (working) week compared to while resting on weekends (Schlotz et al 2004). Age also has an impact, with attenuated amplitudes and increased elevation times in seniors (Van Cauter et al 1995). Another point of disagreement between articles is how to measure cortisol: in plasma, saliva, or urine, and stressors, such as sleep restrictions, can also alter cortisol rhythms, causing periodic exacerbations over a 24-hour period (Hall 2015). Therefore, it would be expected that we would find various results in trials.

Total sleep deprivation over a 1-night period was found to produce various effects on cortisol secretion: an increase during the night itself (von Treuer et al 1996), an increase only in the first half of the night and in the morning (Wright et al 2015), an increase on the night after deprivation (Leproult et al 1997), an increase only in the morning (Vargas & Lopez-Duran; 2020), a decrease throughout the next day (Vgontzas et al 1999), and even no changes (Homma et al 2020). When the deprivation was more prolonged, there was a decrease in cortisol throughout the day (Wright et al 2015), or just in the morning (Choshen-Hillel et al 2021). With partial sleep restriction (< 4 hours), articles report finding: higher cortisol peaks in the morning with lower drops during the day (Kumari et al 2009), lower cortisol peaks in the morning (Detterborn et al 2007), or even no changes to salivary (Zhang et al 2011) and urinary cortisol (Rao et al 2013). When a partial restriction was in place for 2 consecutive days, increased cortisol secretion was found, especially in the afternoon and at night (Guyon et al 2013). Another experiment, with 3 awakenings during 3 consecutive nights, found no change to cortisol levels (Castro-Diehl et al 2014). Therefore, although we found conflicting results in cortisol secretion from disordered sleep, it is a fact that changes occurred in most studies.

Testosterone levels oscillate over a 24-hour period, with higher levels at the beginning of sleep that remain high during the whole sleep period (Luboshitzky et al 1999) and peak after 3 hours when sleep is not interrupted (Luboshitzky et al 2001). Testosterone is not under the influence of the circadian rhythm (it has no association with the day-night cycle), but is related to sleep (Wittert 2014). There are also

contradictory studies related to sleep disorders and testosterone secretion.

With partial sleep restriction (4 or 5 hours), some studies found no differences in testosterone secretion (Smith et al; 2019, Reynolds et al; 2012), whereas others observed a decrease between 2:00 pm and 10:00 pm on the next day (Leproult & Van Cauter 2011). After a single episode of total sleep deprivation, a decrease in testosterone may occur (Cote et al 2013). Nevertheless, it is important to carry out a careful investigation of each patient, because both excess testosterone and testosterone deficits can cause sleep disorders (Barrett-Connor et al 2008; Venancio et al 2008).

Initially, an adequate investigation must be carried out in the athletes, with a detailed anamnesis, physical examination and request for blood tests. Afterwards, the improvement in the quality of sleep is fundamental for the progression in sports performance to occur.

METHOD

This study was approved by the Ethics Committee of the *Irmandade de Misericórdia da Santa Casa de São Paulo*, Brazil, under number 4.402.947, CAAE 39552520.8.0000.5479, and complies with the Declaration of Helsinki for Ethical Principles and Good Clinical Practices established at the XVIII General Assembly of the World Medical Association in 1964. All participants signed a statement agreeing that they had given free and informed consent and had received information about possible adverse effects that could occur during this trial.

Participants and Intervention:

A randomized, double-blind, placebo-controlled trial was performed and we selected 24 participants who exercise at the same CrossFit location, of both genders, between the ages of 25 and 35, whose body mass index (BMI) was between 20 and 24.9 kg/m^2, who complained of difficulty initiating sleep, and presented a total sleep time of less than 6 hours per night. Participants were divided into 2 groups: the experimental group, which received capsules containing 3 mg of melatonin + 1200 mg of GABA (gamma-Aminobutyric acid) (Active Pharmaceutical), and the

control group, which received a placebo (1 g of maltodextrin). The capsules all had the same size and color. Ingestion of the capsules occurred at 10:00 pm, daily, for 8 weeks.
Individuals who matched one or more of the following were all removed from this trial: smokers, anyone who consumed caffeine at > 200 mg/day or any amount after 6 pm, anyone who consumed any amount of alcohol and/or energy drinks after 6 pm, and anyone who used any medication that interfered with sleep. Participants whom we suspected of overtraining were also withdrawn from this study (Savioli et al 2018).
Our participants' work shifts began at 8:00 am and lasted until 5:00 pm or 6:00 pm.
All participants had a diet prescribed by the same dietitian composed of 2 g of proteins, 4 g of carbohydrates, and 1.2 g of lipids per kg of bodyweight.
The participants' only exercise was CrossFit, which they did 4 times a week, in sessions lasting 1 hour each, with 3 workouts during the week at 7 pm and 1 workout on Saturdays at 9 am. They did not perform any other kind of physical exercise besides CrossFit. None of the participants slept in the afternoon, neither during the week nor on the weekend.

Cortisol and Testosterone Evaluation:
Blood samples were collected from all participants, between 8 and 9 am, before our intervention, to measure testosterone and cortisol. Cortisol was measured by an immunoassay using chemiluminescence detection, and testosterone by an immunoassay using electrochemiluminescence. Participants with low/high testosterone or cortisol levels were withdrawn from the study.

Sleep Evaluation:
All participants were evaluated by a physician to assess the duration, frequency of symptoms, and severity of their sleep disorder. Participants who had any other type of sleep disorder that was not defined by difficulty initiating sleep plus presentation of a total sleep time of less than 6 hours per night were withdrawn from this study. To compare each participant before and after our intervention, all participants were assessed using the Pittsburgh Sleep Quality Index (Buysse et al 1989) (PSQI), which consists of 19 self-rated questions and 5 questions rated

by the participant's partner, each of which can range from 0 (no difficulty) to 3 (severe difficulty). A total score greater than 5 indicates that the participant is experiencing a major dysfunction in at least 2 components or a moderate dysfunction in at least 3 components. All participants had a score greater than 5.

Anthropometric Evaluation:

The participants' body measurements were performed by 2 healthcare professionals: a dietitian (examiner 1 - "E1") and a physician specialized in sports medicine and clinical nutrition (examiner 2 - E2). Both examiners had many years of experience measuring skinfolds and circumferences. Lee's equation (Lee et al; 2000) was used to assess each participant's total-body skeletal muscle mass (TBSMM). Examiner 1 used a Sanny® Direct Reading Classic (AD1007-LD) skinfold caliper, while examiner 2 used a Harpenden® Skinfold Caliper. Both examiners used a Sanny® Anthropometric Measuring Tape (TR4010) to measure the participants' circumferences.

The measurements were all performed on 2 mornings (before and after intervention), 2 hours after breakfast, before performing physical activity. Each skinfold and each perimeter of each participant was measured 3 times by each examiner, obtaining an average. This average was used in Lee's equation.

After each examiner calculated Lee's equation, the average of E1 and E2 was used.

Analysis:

The collected data was analyzed using the IBM SPSS Statistics 21 software. The Mann-Whitney test (MW) was used to compare 2 independent groups in the case of quantitative variables. To assess the significance of the group*time interaction, a repeated measures ANOVA was proposed to consider the dependence existing between these 2 measures, before intervention (T0) and after intervention (T1).

RESULTS

The study was completed by 20 participants, 10 from the experimental group and 10 from the control group. Two participants in the control group and 1 participant in the experimental group were unable to perform

the 4 requisite workouts per week and were withdrawn from the study. One participant in the experimental group suffered an orthopedic injury and was also withdrawn from the study. Thus, each group had 10 participants who were evaluated.

The experimental group had an average age of 31.3 ± 2.9 years, a BMI of 24.3 ± 0.6 kg/m^2, and was composed of 7 men and 3 women, while the control group had an average age of 30.7 ± 3.4 years, a BMI of 23.9 ± 0.8 kg/m^2, and was composed of 6 men and 4 women (Table 1).

Table 1: Subjects

Variables		Number		Sig.
		Experimental	Control	
Volunteers		10	10	-
Gender	Male	7	6	-
	Female	3	4	-
Age (years)		31.3 ± 2.9	30.7 ± 3.4	0,89
BMI (kg/m^2)		24.3 ± 0.6	23.9 ± 0.8	0.71

There was a decrease in PSQI scores in both the experimental and control groups. The average initial TBSMM in the control group was 30.5 kg by E1 and 31.1 kg by E2, while in the experimental group it was 27.9 kg by E1 and 28.1 kg by E2. The average final TBSMM in the control group was 30.4 kg by E1 and 30.9 kg by E2, while in the experimental group it was 28.4 kg by E1 and 28.8 kg by E2

Over the 8-week period, E1 found a loss of 100 g of TBSMM in the placebo group, while E2 found a loss of 200 g of TBSMM in this same group. Similarly, over the same 8-week period, E1 found a gain of 500 g of TBSMM in the experimental group while E2 found a gain of 700 g of TBSMM in that same group. Thus, we found similar results between the 2 evaluators (E1 p = 0,538; E2 p = 0,081). The average between the 2 evaluators were a loss of 200 g of TBSMM in the placebo group and a gain of 600 g of TBSMM in the experimental group (p = 0,295). (Table 2, Fig 1 and Fig 2).

Table 2: PSQI and Total-body Skeletal Muscle Mass (TBSMM)

Variables	Number		Sig.
	Experimental	Control	
PSQI TO	12	8	0.008
PSQI T1	5	6	0.77
TBSMM T0 (E1)	27.9	30.5	0.52
TSBMM T1 (E1)	28.4	30.4	0.69

TSBMM T0 (E2)	28.1	31.1	0.45
TSBMM T1 (E2)	28.8	30.9	0.68
TSBMM T0 average	28	30.8	0.60
TSBMM T1 average	28.6	30.6	0.68

PSQI = Pittsburgh Sleep Quality Index
TBSMM = total-body skeletal muscle mass (kgs)
T0 = before intervention
T1 = after intervention
E1 = evaluator 1
E2 = evaluator 2

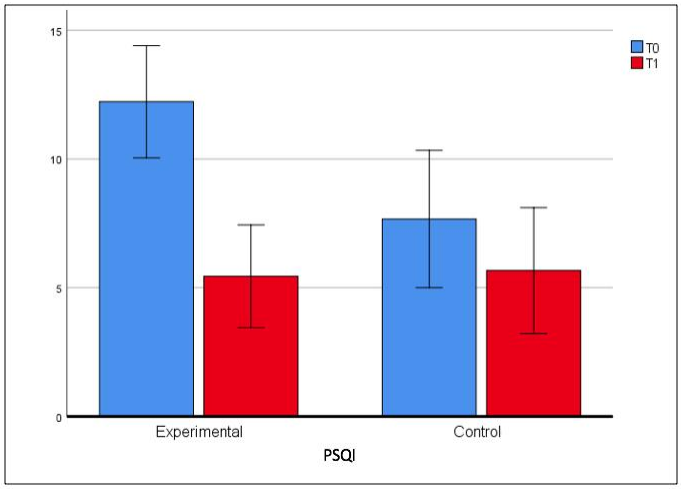

Figure1: PSQI score in T0 and T1 (p = 0.007)

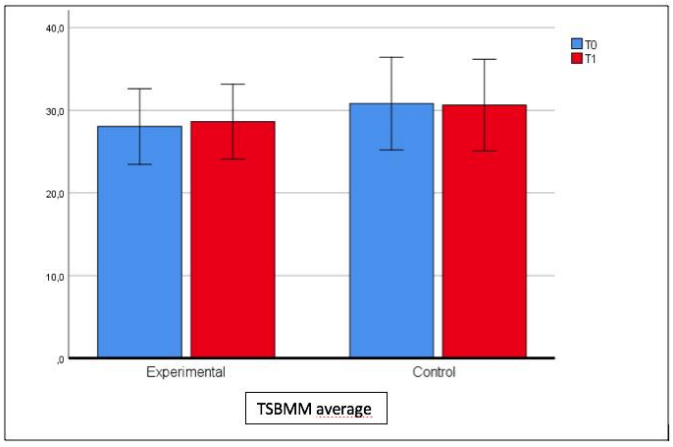

Figure2: TSBMM average in T0 and T1 (p = 0.295)

There was no difference in testosterone and cortisol levels in both groups

Table 3: Testosterone and cortisol

Variables		Number		Sig.
		Experimental	Control	
Testosterone (T0)	**Male**	532.3 ± 122.8	485.3 ± 141.5	0.68
	Female	12.7 ± 4.1	14.1 ± 3.9	0.73
Testosterone (T1)	**Male**	541.5 ± 117.7	455.3 ± 144.8	0.54
	Female	12.9 ± 4.2	13.7 ± 3.5	0.62
Cortisol (T0)		31.3 ± 2.9	14.1 ± 3.3	16.3 ± 2.6
Cortisol (T1)		24.3 ± 0.6	14.5 ± 3.7	18.4 ± 2.1

testosterone in nanograms per deciliter
cortisol in micrograms per deciliter

DISCUSSION

To the best of our knowledge, this is the first study comparing TBSMM with improved sleep quality and duration in a young and physically-active population.

Melatonin is a hormone produced by the pineal gland and is considered a biological marker of night-time (Riha 2018), a chronobiotic that regulates the circadian rhythm. The exogenous melatonin is currently used for secondary sleep disorders supported by empirical evidence (Li et al;2019). Previous studies have demonstrated that melatonin has hypnotic action on secondary sleep disorders (Sadeghniiat-Haghighi et al 2016; Suhner et al 2001; Yoon & Song 2002). However its effectiveness in treating sleep disorders is still under debate.

GABA is the main inhibitory neurotransmitter of the central nervous system. There are two GABA receptors: $GABA_A$ (fast synaptic inhibitor) and $GABA_B$ (slow synaptic inhibitor). Three generations of hypnotics are based on $GABA_A$ receptors (Gottesmann 2002). GABA has been implicated in a large range of behaviors such as anxiety, stress regulation, circadian rhythm and sleep regulation, memory enhancement and perception of pain. (Diana 2014). Low levels of GABA or impaired GABA functioning is associated with the etiology and maintenance of acute and chronic stress (Jie et al 2018), anxiety disorders (Nemeroff 2003)

and sleep disturbances such as insomnia (Gottesmann 2002). Until now, there is limited evidence for sleep benefits of oral GABA intake (Hepsomali et al 2020).

The reason why we prescribed a combination of 3 mg melatonin + 1200 mg GABA for insomnia is because they are highly consumed in most countries due lack of medical prescription.

For a person to gain muscle mass, he or she needs a positive energy balance with adequate nutrient intake (macronutrients and micronutrients) in addition to a favorable hormonal environment for protein synthesis. Sleep restrictions, whether acute or chronic, create a catabolic environment, impairing TBSMM gains or even its maintenance. A study published by Nedeltcheva et al (2010) compared weight loss (caloric intake corresponding to 90% of basal metabolic rate) in participants who slept 5.5 or 8.5 hours/night; of the total weight lost in the group who slept 8.5 hours/night, more than half was from fat, with an average loss of 1.5 kg of fat free mass, while in the group that slept 5.5 hours/night, fat loss represented only a quarter of the total weight loss and average fat free mass loss was 2.4 kg; concluding that adequate sleep is important to preserve muscle mass.

Increase in plasma cortisol contributes, with other hormones, to increase energy expenditure, accelerated net protein breakdown and negative nitrogen balance, increase gluconeogenesis, hyperglycemia and hyperinsulinemia (Tataranni et al 1996). Glucocorticoids also antagonize the action of anabolic regulators such as insulin further exacerbating the loss of protein and muscle mass (Braun & Mars 2015). This situation leads to a catabolic environment which chronically causes muscle atrophy. The first evidence that endogenous glucocorticoids contributed to the process of muscle atrophy came in the observation that adrenalectomized animals failed to undergo muscle atrophy in response to fasting (Wing & Goldberg 1993). Lukas et al (2005) found in nomadic Turkana men a urinary cortisol level inversely related to arm muscle. Pruszkowska-Przybylska et al (2021) evaluated 176 children from 6 to 13 years and concluded that children with a medium concentration of cortisol had higher muscle mass than those with a high concentration of cortisol. Peeters et al (2008) showed that high salivary cortisol is associated with a higher risk of loss of grip strength in older person.

Low testosterone levels are associated with increased fat mass (particularly central adiposity) and reduced lean mass specially in males (Kelly & Jones 2015). In women from 40 to 79 years old, low free testosterone is associated with loss of appendicular muscle mass (Yuki et al 2015).

Although the PSQI results were statistically different before the intervention ($p \leq 0.05$), all participants had a score > 5 and therefore were classified as having major sleep-related dysfunctions.

Gonzalez-Mendoza et al (2019) evaluated 9 different methods of estimating total skeletal mass using skinfolds (Heymsfield, Martin, Doupe, Kerr, Drinkwater, Lee, De Rose, and two equations published by Kuriyan) in professional soccer players and compared these methods with the results observed in dual energy x-ray absorptiometry (DEXA); only Heymsfield's and Lee's methods did not show statistically significant differences compared to DEXA, and Lee's method was considered the most accurate. Knechtle et al (2011) evaluated the total amount of muscle mass in ultra-endurance athletes using both Lee's and Jansen's anthropometric methods and compared them with bioimpedanciometry, noting that only Lee's method showed similar results. A study conducted by Rech et al (2012) also compared skinfold equations for skeletal muscle mass with DEXA, in this case evaluating an elderly population, using Martin's, Doupe's, and Lee's equations, and showed that only Lee's was not statistically different from DEXA.

CONCLUSIONS

The experimental group gained an average of 600 g of TBSMM and the control group lost an average of 200 g in the 8-week period, but this difference was not statistically significant. This trial found no difference between cortisol and testosterone in both groups during 8 weeks. We believe that if the intervention period were longer, and the study conducted with a larger number of participants, it would be possible to find results with a greater difference, which could be statistically significant.

Thus, further studies will be needed to find evidence of gains in TBSMM with improvements to sleep quantity and quality.

Conflict of interest

The authors declared no conflict of interests.

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