ŻAK, Natalia, BŁASZCZYK, Aleksandra, PAŻYRA, Aldona, KUSAK, Natalia, JAWORSKA, Barbara and STANICKI, Paweł. Will melatonin supplementation become a new form of obesity treatment? A review of recent literature. Quality in Sport. 2024;22:54679. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54679
https://apcz.umk.pl/QS/article/view/54679

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 27.08.2024. Revised: 18.09.2024. Accepted: 19.09.2024. Published: 20.09.2024.

Will melatonin supplementation become a new form of obesity treatment? A review of recent literature

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Abstract

Background: In 2020, the World Health Organization (WHO) estimated that 650 million adults worldwide are obese, and 2.8 billion individuals struggle with overweight. Obesity is associated with an increased risk of cardiovascular diseases, type 2 diabetes, heart disease, adverse effects on mental health, the development of certain cancers, and other conditions. In recent years, there has been growing interest in the role of melatonin, which has therapeutic potential in the treatment of obesity. Studies suggest that melatonin supplementation may lead to weight reduction and improvement in metabolic parameters, significantly reduce cardiovascular disease risk factors, and enhance insulin sensitivity in obese individuals.

Aim of study: This review aims to present the latest scientific findings on the impact of melatonin supplementation on the development of obesity and its complications. We focus primarily on the mechanisms of melatonin's action in the context of obesity, particularly on potential pathways that have not yet been thoroughly explored. Our aim is to provide deeper insights into research on obesity and its prevention.

Materials and Methods: Search was conducted using PubMed and Google Scholar databases, utilizing the keywords "obesity," "melatonin," and "weight loss" in various configurations. The review primarily considers studies published after 2016 that are available online.

Summary: Melatonin supplementation leads to a statistically significant reduction in blood glucose levels and an increase in cellular insulin sensitivity. Its promising properties in the treatment of obesity have been demonstrated through the reduction of oxidative stress, indicating a potential adjunct for weight loss. Based on the cited studies, the beneficial effects of melatonin supplementation on cardiovascular risk factors have been confirmed. Melatonin could be considered as an adjunctive therapy for obese individuals who do not respond to other treatment modalities.

KEYWORDS: obesity, melatonin, BMI, weight loss

Introduction:

Obesity has emerged as a significant global health crisis. It is now established that one-third of the world's population, amounting to over 2 billion people (1), are affected by overweight or obesity. The development of obesity is influenced by various factors, including excessive caloric intake relative to energy requirements, low physical activity, sedentary lifestyle, and genetic predisposition (2). The diagnosis of overweight and obesity is conducted by measuring weight and height, followed by calculating the body mass index (BMI): weight (kg) / height^2 (m^2). BMI serves as a proxy indicator of body fat, and additional measurements, such as waist circumference, can further support the diagnosis of obesity. According to the World Health Organization (WHO), obesity is defined as a BMI of 30 or higher (Table 1).

BODY MASS INDEX (BMI)

BMI	CLASSIFICTION
< 18,5	underweight
18,5-24,5	healthy weight
25,0- 29,9	overweight
30,0- 34,9	obesity class I
35,0-39,9	obesity class II
≥ 40,0	obesity class III

Table 1. BMI Classification (3)

In 2019, approximately 18.5% of adults in Poland were affected by obesity, a rate higher than the European average of 16% (4). The International Agency for Research on Cancer (IARC) recognizes obesity as a cause of at least 13 different types of cancer (5). Projections indicate that in some countries, obesity may surpass smoking as the leading cause of cancer in the coming decades. According to data collected in 2022, it is estimated that at least 40% of cancer cases could potentially be prevented, with smoking and obesity emerging as the two most significant modifiable causes of cancer (6).

Obesity can also lead to a range of other dysfunctions, such as type 2 diabetes, dyslipidemia, non-alcoholic fatty liver disease (NAFLD), and cardiovascular diseases (7,8), making obesity and its complications a critical health issue. Obesity results from complex interactions between genetic, socioeconomic, and cultural factors. Consumption patterns, urban development, and lifestyle habits significantly influence the prevalence of obesity. It has been observed that individuals with obesity experience lower quality of life and work efficiency, which translates into reduced potential earnings and higher healthcare costs, thereby placing a financial burden on society (2,9). Therefore, there is an urgent need for effective strategies to stop the progression of obesity.

Melatonin is the principal hormone produced by the pineal gland in vertebrates. Its synthesis exhibits a pronounced circadian rhythm and shows seasonal variations. Peak serum levels of melatonin consistently occur during the night, regardless of whether the species is diurnal or nocturnal (10). The circadian rhythm of melatonin is maintained throughout the year, but its production is significantly higher during short winter photoperiods compared to long summer photoperiods. The increased melatonin production during the winter is primarily due to the extended nocturnal peak of secretion. This daily rhythm of melatonin secretion is directly linked to its release by the pineal gland, as evidenced by the fact that this rhythm is abolished following pinealectomy (11). In mammals, the rhythm of melatonin is generated by the central circadian clock located in the suprachiasmatic nuclei (SCN) of the hypothalamus. The SCN synchronizes with the 24-hour day-night cycle, receiving light signals directly from the retina. It then transmits signals through a multi-synaptic neural pathway to the pineal gland, driving the rhythmic production of melatonin (12). Melatonin is now recognized as a pleiotropic hormone with significant effects on the circadian rhythm (13), the immune system (14,15), carcinogenesis (16), and energy metabolism (17). Considering that melatonin is a potential regulator of metabolism, its relationship with obesity has been discussed in the literature (18–20). This includes exploring the role of melatonin in the regulation of obesity, as well as mechanisms such as its antioxidant and anti-inflammatory effects.

State of Knowledge:

As early as 1984, Bartness et al. (21) demonstrated that disrupted circadian rhythms led to weight gain in hamsters subjected to pinealectomy, suggesting a link between the pineal gland, melatonin, and body weight. Subsequent research has confirmed that exogenous melatonin supplementation reduces body weight in animals (22). Melatonin has been shown to inhibit weight gain and the accumulation of visceral fat, particularly in animals fed high-fat/high-sugar diets. In a study conducted by Szewczyk-Golec et al. (23), melatonin supplementation (10 mg/day before sleep) was combined with a caloric-restricted diet (1000-1200 kcal/day for women and 1400-1600 kcal/day for men) over a 30-day period in adults with obesity. Melatonin facilitated a reduction in body weight from 113.6 kg to 105.9 kg, compared to the placebo group, which experienced a reduction from 114.4 kg to 109.8 kg. Additionally, the level of malondialdehyde (MDA), an indicator of oxidative stress, was measured and found to be lower in the melatonin group, decreasing from 34.3 to 24.5 nmol/g Hb, whereas in the placebo group, it decreased from 30.1 to 27.4 nmol/g Hb.

The reduction in oxidative stress observed in the study suggests potential therapeutic benefits of melatonin in patients with obesity, where increased oxidative stress may be associated with the risk of insulin resistance and visceral fat accumulation (24). Walecka-Kapica et al. (25) demonstrated a significant reduction in body mass index (BMI) in postmenopausal women (mean age 56.9 ± 5.3) with both excessive (from 29.62 to 27.88 kg/m²; p<0.001) and normal (from 22.07 to 21.86 kg/m²; p<0.05) body weight after a 24-week therapy combining melatonin supplementation (5 mg/day) with a balanced diet of 1500 kcal/day. In addition to changes in body composition, participants receiving melatonin reported improvements in sleep quality, as assessed by the Insomnia Severity Index (ISI). Melatonin supplementation led to a reduction in body weight among women with excess weight, with BMI decreasing from 29.62 ± 3.69 to 27.88 ± 3.14 after 16 weeks ($p < 0.001$). A tendency towards weight reduction was also observed among patients who were not overweight.

A notable study conducted by McFadden et al. (26) in the United Kingdom in 2014 investigated the relationship between various anthropometric parameters and light exposure during sleep. This analysis, which included over 113,000 women, found that metrics such as Body Mass Index (BMI), Waist-to-Hip Ratio (WHR), Waist-to-Height Ratio (WHtR), and waist circumference increased proportionally with the amount of light in the room where the women slept at night.

These associations persisted even after accounting for factors such as age, socioeconomic status, alcohol consumption, intense physical activity, night shift work, having young children, sleep duration, and smoking. The British findings are consistent with an earlier study from Japan (19), which investigated the impact of nighttime artificial light exposure (LAN) on obesity development. This study found that individuals sleeping in brighter rooms had higher body weight, waist circumference, and BMI. Furthermore, animal experiments demonstrate that increased light exposure can affect metabolic regulation and lead to an increase in adipose tissue (27) and body weight, even with constant caloric intake and daily activity levels (28). According to Polish researchers (29), the use of melatonin (5 mg/day, two hours before bedtime) in thirty patients with metabolic syndrome, who did not respond to three months of lifestyle changes, resulted in improvements in LDL cholesterol levels and blood pressure within just two months. Additionally, melatonin was found to reduce nocturnal hypertension, improve both systolic and diastolic blood pressure, lower the pulsatility index in the internal carotid artery, decrease platelet aggregation, and reduce serum catecholamine levels (30,31). A meta-analysis and systematic review conducted by researchers from the Chinese University of Hong Kong demonstrated that melatonin supplementation reduced nocturnal systolic blood pressure by 3.57 mm Hg (31). Cai et al. (32) found that low endogenous melatonin levels were associated with decreased long-term survival in patients with pulmonary hypertension. Several mechanisms underlying the pleiotropic effects of melatonin have been identified, including its antioxidant, anti-inflammatory, vasodilatory, cardioprotective, anti-cancer properties, and its benefits in the treatment of respiratory diseases. In patients with pulmonary hypertension, melatonin levels were correlated with excessive activation of the sympathetic nervous system and/or the renin-angiotensin system. Further studies have demonstrated that melatonin improves treatment outcomes in patients with heart failure and is considered both a preventive and adjunctive therapy [30].

A randomized, double-blind, placebo-controlled clinical trial, in which patients with heart failure and reduced ejection fraction were administered 10 mg of oral melatonin daily for 24 weeks, revealed improvements in endothelial function (33).
There have been suggestions that melatonin may play a significant role in managing blood glucose levels, particularly in cases of insulin-independent type 2 diabetes. In a small placebo-controlled study conducted on men with diabetes, a 12% reduction in insulin sensitivity was observed after a three-month treatment with 10 mg of melatonin daily (34). It is highly probable that differences in the effect of melatonin on oral glucose tolerance may be related to polymorphisms in the melatonin receptor 1B gene (MTNR1B), which are associated with type 2 diabetes (35). Early studies on pinealectomy have shown that the absence of melatonin secretion leads to glucose intolerance and insulin resistance (36). Interestingly, reintroducing exogenous melatonin into this system restored metabolic parameters to levels observed in control animals. Similarly, in mice fed a high-fat diet (HFD), administration of exogenous melatonin was sufficient to reverse reduced insulin sensitivity and glucose tolerance (37). Consequently, another study found that daily melatonin administration reduced weight gain in HFD-fed rats by 54% compared to HFD-fed rats not receiving melatonin (38).

Summary:
Melatonin supplementation shows promise as a therapeutic agent for obesity and its complications due to its biological effects on insulin metabolism and adipose tissue, as well as its antioxidant and anti-inflammatory properties. Melatonin has been suggested as an adjunctive treatment for obesity and associated metabolic disorders, including type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), hypertension, and dyslipidemia. However, the role of melatonin as an adjunct for weight loss remains a topic of debate, as does its safety. Current evidence suggests that melatonin has potential for reducing body weight, although further research is needed to confirm its clinical efficacy. Dosage and duration of melatonin administration should be considered as factors in determining its effectiveness as a treatment option.

Disclosure:
Author’s Contribution
Conceptualization: N. Żak. Methodology: A. Błaszczyk. P. Stanicki Software: B. Jaworska Check: A. Pażyra. Formal Analysis: ; Investigation: N. Kusak, A. Pażyra.
Resources: N. Żak, A. Pażyra, N. Kusak. Writing –Rough Preparation: B. Jaworska, P. Stanicki Writing –Review and Editing: N. Żak, A. Błaszczyk Supervision: B. Jaworska, A. Błaszczyk, N. Kusak Project Administrator: N. Żak, P. Stanicki
All authors have approved the submission of the manuscript.

Funding Statement: The study did not receive special funding.

Institutional Review Board Statement : Not Applicable.

Informed Consent Statement : Not Applicable

Data Availability Statement : Not Applicable

Conflict of Interest Statement: The authors declare no conflict of interest.

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