Review Article

Therapeutic Potential of melatonin as an anti-obesity agent Melatonin as an anti-obesity agent

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ABSTRACT

Obesity is a major healthcare crisis, with the number rising each year, which is concerning. Obesity is associated with many metabolic syndromes, heightening the risk of Type 2 diabetes mellitus, cardiovascular diseases, stroke, fatty liver, and hypertension. This imposes a substantial burden on healthcare systems, with escalating annual costs. Current management strategies for obesity include lifestyle interventions, bariatric surgery, and pharmacotherapy. Lifestyle management often results in modest weight loss. Bariatric surgery, while effective in achieving significant weight loss, is limited by risks and accessibility. Different FDA-approved pharmacotherapies are also available, but there are some limitations. Emerging research highlights melatonin as a promising therapy for obesity treatment due to its multifaceted mechanisms. Melatonin's potential benefits include regulating metabolic processes, suppressing appetite, improving insulin sensitivity, exhibiting antioxidant and anti-inflammatory effects, and modulating circadian rhythms. Recent studies suggest that melatonin supplementation may contribute effectively to obesity management by impacting weight loss, appetite regulation, and insulin resistance. This review aims to evaluate the physiological effects of melatonin in obesity therapy, focusing on its impact on metabolic health, appetite control, and insulin sensitivity while acknowledging the need for further research in this area.

Key words: Anti-obesity agents, Basal metabolic index (BMI), Insulin resistance, Obesity, Melatonin, Metabolic syndrome

Obesity has become a challenging global public health crisis. Since 1990, the prevalence of obesity has increased by 700 million, making the current number 890 million. America has experienced the most significant increase in prevalence, affecting one-third of adults in 2022.[1] According to the World Health Organization (WHO), obesity is characterized as an abnormal or excessive accumulation of fat that poses health risks.[2] Body Mass Index (BMI) is used to categorise obesity (Table 1), with individuals having a BMI of 30 or higher classified as obese, further divided into Class I (30-34.5), Class II (35-39.5), and Class III (≥40) [3]

Obesity-related metabolic syndromes increase the likelihood of multiple diseases, including Type 2 diabetes mellitus, cardiovascular diseases, stroke, fatty liver, hypertension, and impose a high burden on the healthcare system with annual costs ranging from $2,505 more or 100% more, compared to those with average weight. This cost rises significantly with the class of obesity, increasing by 68.4% for class 1 to 233.6% for class 3. [4,5]

Current treatment options for obesity are very limited, including lifestyle management, bariatric surgery, and pharmacotherapy. Most lifestyle management includes partial or total meal replacement, intensive behaviour therapy, and structured exercise, which typically help to achieve only 10% of weight loss.[6] Bariatric surgeries are currently the most widely used alternative with benefits such as inducing and maintaining ≥15% weight loss, reducing appetite, and improving obesity-related complications. However, they carry

Table 1: WHO criteria for diagnosing obesity across different age groups

Age group	Diagnosis of obesity by WHO
<5 years	Weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median
5 to 19 years	Greater than 2 standard deviations above the WHO Growth Reference median
Adults	BMI greater than or equal to 30

Source of data: WHO [3]

Access this article online

Received – 29th September 2025
Initial Review – 10th October 2025
Accepted – 22nd October 2025

DOI: 10.32677/ejms.v10i4.7888

Quick Response code

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risks and complications during the postoperative period, limited surgical capacity, and patient fitness issues make it difficult to operate on everyone [7,8]. Lastly, FDA-approved pharmacotherapies for short-term obesity management include orlistat, phentermine-topiramate, Naltrexone-bupropion,

liraglutide, and semaglutide, with only 5-10% of mean weight loss, except for semaglutide, which has been shown to reduce up to 14.9% weight loss in obese people with diabetes. [9,10]

These challenges highlight the need for more promising, safer, and effective strategies to control and reduce the rising incidence of obesity. Melatonin plays a role here as an endogenous hormone derived from tryptophan and synthesised by the pineal gland in vertebrates. Its synthesis is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, allowing melatonin to express a circadian rhythm aligned with the light-dark cycle.[11] Melatonin is approved as a dietary supplement in the United States by the FDA, and its over-the-counter sales have doubled between 2017 and 2020 [12]. Its receptor agonists (Ramelteon, Circadin, Agomelatine, etc.) are being widely used for the therapeutic management of insomnia, depression, and circadian rhythm sleep-wake disorders.[13]

Ramelteon is the first FDA (2005) approved melatonin agonist in the USA, as it is well tolerated, has negligible adverse effects, and no rebound insomnia or withdrawal effects on discontinuation. Apart from its role in the sleep-wake cycle, melatonin also exhibits other promising effects, such as antioxidant, anti-inflammatory, and free radical scavenging properties.[14,15] This review explores the potential of melatonin in addressing obesity, examining various mechanisms and effects in detail.

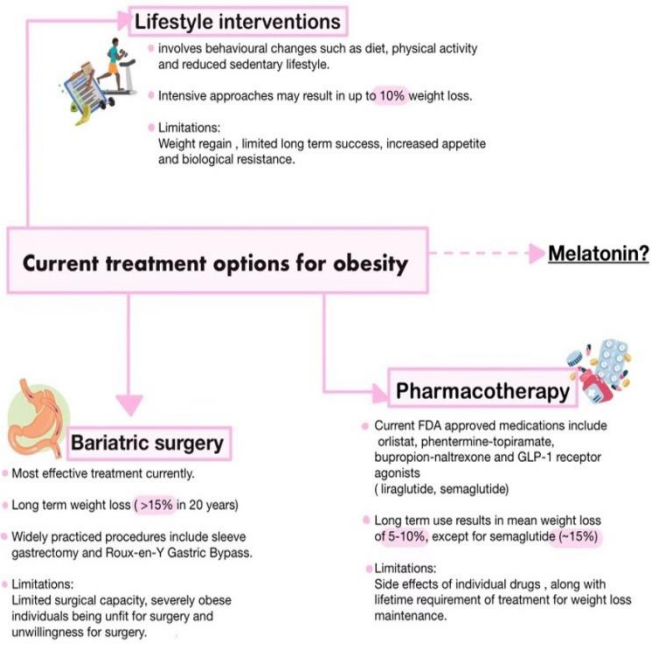

Figure 1: Current Treatment Options for Obesity[6, 7, 8, 9, 10]

Pathophysiology

Melatonin may function as an anti-obesity agent through various mechanisms, and work together to promote the browning of fat, reduce white adipose tissue, lower overall fat levels, and increase lean muscle mass.[16]

Metabolic Effects of Melatonin

Thermogenesis in brown adipose tissue

Melatonin leads to enhanced thermogenesis through its notable metabolic effects on brown adipose tissue (BAT). Firstly, melatonin increases uncoupling protein 1 (UCP1) expression in BAT [17], a key marker of thermogenic activity [18]. There are three reported mechanisms through which melatonin acts on brown adipose tissue to increase UCP 1 expression. This includes a central pathway stimulating MT1 receptors located within the hypothalamus, a peripheral pathway that directly acts on MT1 and MT2 receptors located on brown adipose tissue, and an alternative pathway involving its interaction with various hormones, such as thyroid hormones, leptin, and insulin.[19]

MT1 and MT2 stimulation commonly leads to reduced intracellular cyclic adenosine monophosphate (cAMP). This further affects protein kinase A(PKA) activity and the phosphorylation of cAMP-response element binding protein (CREBP), leading to increased UCP 1 expression, which ultimately dissipates energy in the form of heat by uncoupling mitochondrial respiration.[18,20] In addition, melatonin led to an increase in fibroblast growth factor 21 (FGF21) levels, further upregulating Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) in BAT, contributing to increased fat utilisation and thermogenesis. [21, 22]

White Adipose Tissue Browning

Melatonin can promote "browning" of white fat, i.e., the appearance of brown, thermogenic adipocytes within White adipose tissue. It does this by (1) encouraging existing white adipocytes to adopt brown-like features and (2) steering mesenchymal precursors toward brown adipocytes. The result is higher expression of thermogenic markers such as UCP1**,** CITED1, and PGC-1α**,** with a parallel reduction in white-fat markers (e.g., ASC-1**).** Melatonin's action likely involves MT1/MT2 signalling and increased sympathetic drive to adipose tissue, which together favour heat-producing metabolism over energy storage.[23,24]

Mitochondrial regulation

Melatonin stimulates mitochondrial biogenesis, particularly in brown adipose tissue (BAT) and skeletal muscle. In BAT, melatonin improves mitochondrial function by increasing the respiratory control ratio (RCR), indicating better energy efficiency through reduced proton leak during respiration. It also raises the phosphorylation coefficient (ADP/O) ratio, enhancing ATP production and reducing cellular stress. One of the key protective effects of melatonin is its ability to

lower **oxidative** and nitrosative stress**.** [19] Nitrosative stress refers to cellular damage caused by an excess of reactive nitrogen molecules—mainly *peroxynitrite*—formed when nitric oxide combines with superoxide radicals. These reactive compounds can damage proteins, lipids, and mitochondrial enzymes, leading to impaired energy production. Melatonin counters this by scavenging these harmful molecules and boosting antioxidant enzymes such as superoxide dismutase, which helps neutralize free radicals. [25]

In addition, melatonin prevents the opening of the mitochondrial permeability transition pore (mPTP), a channel that can collapse the mitochondrial membrane potential under stress. .[26] In skeletal muscle, melatonin activates the CaMKII/AMPK/PGC-1α pathway, which increases the expression of thermogenic and mitochondrial biogenesis genes such as PGC-1α, PPARγ, and NRF1. It also enhances the uncoupling of sarcolipin (SLN) from the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2), promoting non-shivering thermogenesis and further supporting mitochondrial growth and energy metabolism. [25]

Appetite suppression and effect on insulin sensitivity

Effects on appetite

Melatonin can have regulatory effects on appetite through its modulation of the expression of appetite-related genes. Melatonin upregulates the expression of anorexigenic genes such as leptin and proopiomelanocortin (POMC). It downregulates the expression of orexigenic genes such as ghrelin, orexin, and neuropeptide Y**.**[27] Melatonin also curbs overeating and excessive hunger by improving insulin action and stabilising blood glucose levels.[28]

Insulin resistance

Melatonin improves insulin resistance through the combined effects of reduced inflammation in adipose tissue and increased adenosine monophosphate kinase (AMPK) signalling. Increased AMPK activity leads to activation of carnitine palmitoyltransferase I (CPT1) and peroxisome proliferator-activated receptor alpha (PPAR-α), the main enzymes involved in fatty acid oxidation. This leads to better glucose uptake and utilisation, decreasing the likelihood of fat deposition.[29] Melatonin also increases the expression of the Protein Kinase B (PKB) gene and protein, which is a central component of the Phosphoinositide 3-Kinase/AKT serine/threonine kinase (PI3K/AKT) insulin signalling pathway, contributing to glucose homeostasis and improved insulin sensitivity.[30]

Additionally, melatonin led reprogramming of the gut microbiota causes a reduction in faecal levels of short-chain fatty acids, including acetic acid, butyric acid, isovaleric acid, caproic acid, and isobutyric acid, the levels of which are positively correlated with increased insulin resistance. Hepatic genes involved in gluconeogenesis, including fructose-1,6-bisphosphatase 1, forkhead box O1 alpha, thioredoxin-interacting protein, phosphoenolpyruvate carboxy-kinase (PEPCK), PEPCK1, and a glucose-6-phosphatase catalytic subunit, are also downregulated under the influence of melatonin.[31]

Anti-oxidant and Anti-inflammatory Roles

Anti-oxidant

Obesity creates a pro-inflammatory state, and persistent inflammation is considered a major risk factor for developing obesity-related metabolic complications, including diabetes, stroke, cardiovascular disease, etc.[32] Melatonin can directly interact with reactive oxygen species, leading to their elimination. The aromatic indole ring of melatonin directly buffers reactive oxygen species(ROS) and reactive nitrogen species(RNS).[33] Melatonin also indirectly leads to the upregulation of several anti-oxidant enzymes involved in glutathione metabolism, preventing mitochondrial damage and protecting organs such as the liver, pancreas, and adipose tissue from oxidative stress.[34]

MT1 and MT2 stimulation leads to increased expression of antioxidant enzymes, including catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase.[35] Melatonin also acts by inducing nuclear factor erythroid 2-related factor 2(Nrf2), an oxidative stress sensor which increases the antioxidant defences by binding to antioxidant response elements (AREs).[36] Melatonin also causes upregulation of silent information regulator 1/Sirtuin 1 (SIRT1) leading to p53 deacetylation. This reduces p53 activity and, therefore, reduces the cellular stress response and production of reactive oxygen species.[37]

Anti-inflammatory

Diabetes, hypertension, and other metabolic diseases are linked to an increase in systemic inflammatory response to fat deposition in adipocytes. Melatonin decreases pro-inflammatory cytokines such as interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and monocyte chemotactic protein-1 (MCP-1).[38] Melatonin upregulates SIRT-1, which subsequently inhibits activation of nuclear factor kappa B (NF-κB) and the nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) inflammasome.[39] Failure of NLRP3 activation leads to decreased levels of pro-inflammatory cytokine Interleukin-1 beta (IL-1β) and prevents caspase-1 activation, reducing apoptosis related to inflammation.[40] Moreover, melatonin inhibits myeloperoxidase, nitric oxide synthase, and cyclooxygenase-2, some key pro-inflammatory enzymes.[33]

Circadian rhythm regulation

Effect on the sleep-wake cycle

Short sleep duration is significantly associated with the risk of developing obesity in human adults.[41] Melatonin protects

against sleep deprivation-induced obesity by increasing liver ampkα/pparα signaling, which leads to increased lipid breakdown and decreased fat deposition.[42] Melatonin also acts via MT1 receptors to inhibit orexin neurons in the lateral hypothalamus and promote sleep,[43] thereby regulating both sleep and appetite.

Effect on biological clock genes

Melatonin prevents the desynchronisation of biological clock genes induced by high-fat dietary intake.[44] Circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1) are the main circadian genes crucial for the regulation of metabolism under the influence of melatonin. Melatonin helps in the regulation of carbohydrate metabolism, lipid metabolism, and triglyceride levels through its actions on CLOCK and BMAL1.[45]

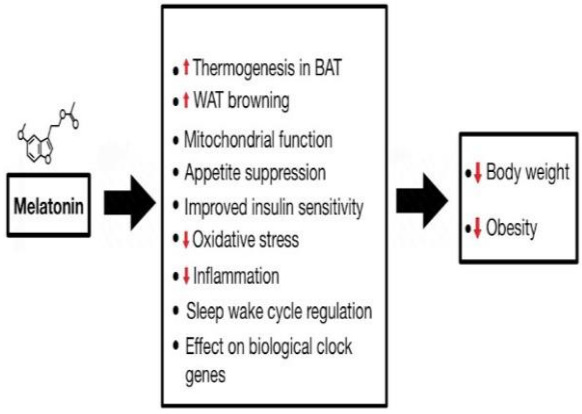

Figure 2: Mechanism of melatonin as an anti-obesity agent[16-18]

DISCUSSION

Melatonin may serve as an adjunct in obesity management. Across preclinical models, melatonin enhances thermogenesis (via BAT activation and WAT browning), improves mitochondrial efficiency, attenuates oxidative and inflammatory stress, and stabilizes circadian signals that regulate appetite and energy expenditure. Clinical studies report modest improvements in weight, waist circumference, body composition, lipid parameters, sleep quality, and insulin resistance, especially when melatonin is combined with dietary and lifestyle interventions.[46] Recent studies have investigated various pharmacological tools for obesity management, with promising evidence suggesting that melatonin supplementation may serve as an effective therapeutic approach.[47]

Weight loss/BMI/Waist circumference:

A 2023 study by Gitti et al. revealed significant reductions in body weight and BMI for both the melatonin and control groups, with more pronounced weight loss observed in the melatonin group.[47] This study also reported a notable decrease in waist circumference and improvements in insomnia severity among patients receiving melatonin treatment.[48]

Additionally, a systematic review and meta-analysis encompassing 23 studies found that 11 studies indicated beneficial outcomes from melatonin supplementation regarding weight loss, BMI, and waist circumference compared to placebo. Notably, melatonin decreased weight gain induced by standard treatments (like Olanzapine and lithium carbonate) and was more effective in children and adolescents.[49]

In research conducted in Iran by Mohammadi, significant reductions in body weight and BMI were observed in both the melatonin and placebo groups; however, waist circumference reductions were statistically significant only in the melatonin group. Furthermore, a notable decrease in body fat percentage was seen only in the melatonin group.[50]

An investigation combining melatonin supplementation (10 mg/day, 1 hour before bedtime) with a calorie-restricted diet in adult obesity patients found that the melatonin group experienced enhanced weight loss compared to the placebo group, alongside a significant reduction in malondialdehyde (MDA) levels, a biomarker of oxidative stress. [51]

In another randomised clinical trial by Amstrup et al. (2016), postmenopausal women with osteopenia receiving melatonin (1 and 3 mg/day) for 12 months showed improvements in body composition, with a 6.9% reduction in fat mass and a 5.2% increase in lean mass compared to the placebo group. [52]

Two meta-analyses have evaluated clinical trials on body composition and melatonin supplementation. Mostafavi et al. (2017) found that melatonin supplementation alone was ineffective for weight loss but showed positive effects when combined with other interventions.[53] A more recent meta-analysis published in 2019 supported these findings, indicating that while melatonin improved certain lipid biomarkers, it did not facilitate weight loss when used solely. [54]

Walecka-Kapica et al. (2014) observed a significant reduction in BMI among postmenopausal women undergoing a combined therapy of melatonin supplementation (5 mg/day for 24 weeks) and a balanced diet (1500 kcal/day). Participants also reported improved sleep quality as measured by the insomnia severity index (ISI).[55]

Lastly, a study by Kozirog et al. (2011**)** demonstrated that melatonin (5 mg daily) administered for one month effectively reduced body weight and BMI in patients with metabolic syndrome.[56] Among the 33 healthy volunteers and 30 patients who did not respond to lifestyle modifications, melatonin treatment significantly improved the lipid profile (decrease in LDL-C) and lowered blood pressure, alongside the weight loss benefits.

Lipid marker:

The 2019 systematic review and meta-analysis by Loloei et al. found that melatonin supplementation notably reduced triglyceride and LDL cholesterol (LDL-C) levels. However, it did not have a significant impact on body mass index (BMI), weight, waist circumference (WC), or HDL cholesterol (HDL-C).[54]

Similarly, another systematic review and meta-analysis revealed that melatonin supplementation significantly improved triglyceride and total cholesterol. It did not significantly affect LDL-C or HDL-C levels. Also found that the benefits were more pronounced with higher doses and longer durations of treatment.[57]

In a 2014 study, melatonin and its precursor tryptophan were associated with reduced levels of triglycerides and LDL-C after 14 months of therapy. No significant changes were observed in total cholesterol or HDL-C levels over the same period.[58]

Insulin resistance:

A systematic review of 15 randomized controlled trials (RCTs) found that melatonin supplementation at a dose of 10 mg significantly lowered homeostasis model assessment of insulin resistance (HOMA-IR) levels in individuals with various health conditions.[59] Another systematic review and meta-analysis from 2021 reported that melatonin administration effectively reduced insulin levels and HOMA-IR while increasing the quantitative insulin sensitivity check index (QUICKI). The findings indicated that melatonin improved hyperinsulinemia, insulin resistance, and insulin sensitivity.[60]

Additionally, a study by Sun et al. (2018) demonstrated that after 12 weeks of melatonin treatment at 3 mg per day, there were significant reductions in HOMA-IR (from 8.99 ± 5.10 to 7.77 ± 5.21, $p < 0.05$) and fasting insulin levels (from 37.09 ± 20.26 μU/ml to 32.10 ± 20.29 μU/ml, $p < 0.05$). Significant improvements were also observed in Acanthosis Nigricans scores, body weight, BMI, body fat, visceral index, neck circumference, waist circumference, and inflammatory markers.[61]

Appetite regulation:

Bahrami et al. (2019) reported that melatonin supplementation led to a reduction in serum leptin levels without altering total calorie intake or the proportions of macronutrients. They assessed dietary intake using 24-hour food recalls and noted a significant decrease in food consumption following melatonin treatment.[62] Buonfiglio et al. (2018) observed a decrease in food intake after a nine-week melatonin intervention[63], whereas Farias et al. (2019) found no significant changes in food intake following their intervention.[64] Taheri et al. (2019) investigated the impact of melatonin on metabolic hormones and found significant reductions in both leptin and ghrelin levels after supplementation.[65] Nogueira et al. (2022) noted that melatonin administration did not lead to significant changes in total energy intake, macronutrient distribution, types of foods consumed, or meal timing. Additionally, variations in circadian misalignment and chronotype did not affect these outcomes.[66]

Melatonin may function as an anti-obesity agent through various mechanisms, such as regulating metabolism, controlling appetite, enhancing insulin sensitivity, and providing antioxidant and anti-inflammatory benefits, as well as modulating circadian rhythms. Studies demonstrate that melatonin enhances adipose thermogenesis, supports mitochondrial efficiency, modulates inflammatory and oxidative balance, influences appetite regulation, and promotes circadian alignment. Clinical data derived mainly from small randomized controlled trials (RCTs) and meta-analyses indicate modest but reproducible improvements in weight, waist circumference, body composition, insulin resistance, and select lipid markers.

The effects appear stronger when melatonin is combined with calorie restriction or sleep optimization. Melatonin is inexpensive, easily accessible, and generally well tolerated. When taken 1–2 hours before habitual bedtime, it may serve as a useful adjunct in managing obesity, especially in patients with short sleep duration, circadian misalignment, insomnia, or evening hyperphagia. Nonetheless, standard-of-care interventions including diet, physical activity, behavioural modification, and, when indicated, pharmacotherapy or bariatric surgery remain the primary treatment.

Although more investigations are required, we provide evidence for the use of melatonin as an adjuvant treatment for obesity and other metabolic syndromes. Existing trials differ in dose (1–10 mg), formulation, timing, duration, and study populations. Most are small and of short duration. Anthropometric benefits are modest and inconsistent; some analyses show metabolic improvements without significant weight reduction. Long-term efficacy and safety, optimal dosing and timing, and potential interactions with newer anti-obesity agents (e.g., GLP-1/GIP receptor agonists) remain unclear. Large, long-term RCTs incorporating standardized sleep and circadian metrics are warranted to clarify melatonin's role in metabolic management.

CONCLUSION

Obesity remains a complex, multifactorial disease with rising prevalence and substantial clinical and economic burden. Melatonin, a circadian hormone, has biologic plausibility as an adjunct therapy. Across various experimental models, melatonin enhances brown fat thermogenesis and brown fat formation, improves mitochondrial efficiency, and reduces oxidative and inflammatory stress. It also modulates appetite pathways and stabilizes circadian timing, mechanisms that

plausibly support healthier energy balance. Clinical evidence remains heterogeneous but suggests modest, clinically relevant improvements in weight, waist circumference, body composition, lipid parameters, sleep quality, and insulin resistance, particularly when melatonin is combined with diet, activity, and sleep hygiene measures. Safety profiles are generally favourable at commonly used doses; however, long-term data in individuals with obesity and multimorbidity are limited.

Future work should prioritize adequately powered, longer-duration randomized trials that standardize dose, timing (relative to dim-light melatonin onset and sleep), and outcome measures, incorporating circadian and sleep endpoints, and evaluating melatonin's role alongside modern anti-obesity agents and bariatric pathways.

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Funding: Nil; Conflicts of Interest: None Stated.

How to cite this article: Dhalani M, Malik A, Dahiya S, Aggarwal K, Jain R. Therapeutic Potential of melatonin as an anti-obesity agent Melatonin as an anti-obesity agent. Eastern J Med Sci. 2025; 10(4):115-121.