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REVIEW ARTICLE

Melatonin and treatment of patients with obesity and meta-inflammation: a meta-analysis

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Abstract

Introduction: According to the World Atlas of Obesity, overweight and obesity will affect nearly 3 billion adults (approximately 50% of the global adult population) by 2030. Melatonin therapy (MEL) and its pharmacological analogues are notable therapeutic agents for treating various pathologies, including obesity, metabolic diseases, and diabetes. **Objective:** A meta-analysis of melatonin therapy in the treatment of patients with obesity and meta-inflammation was conducted. **Methods:** The PRISMA systematic review guidelines were followed. Randomized clinical trials, prospective studies, and retrospective studies were included in the analysis. The literature search was conducted from July to August 2025 and was based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present. **Results and Conclusion:** Eighteen clinical studies with 4,678 participants were selected for this meta-analysis. According to the GRADE instrument, most studies presented homogeneous results, with X^2=96.8%>50%. Considering the Cochrane risk of bias tool, the overall assessment resulted in 20 studies with a high risk of bias and 24 studies that did not meet the GRADE and AMSTAR-2 criteria. It was concluded that melatonin supplementation with an average of 5.0 mg significantly reduced body weight and reduced comorbidities in patients with obesity and meta-inflammation. Melatonin also regulates food intake, regulating the production and secretion of insulin, glucagon, and cortisol, and plays an important role in insulin signaling, with its deficiency having diabetogenic effects.

Keywords: Obesity. Weight loss. Inflammatory processes. Metabolic syndrome. Melatonin.

Introduction

According to the World Obesity Atlas, overweight and obesity will affect nearly 3 billion adults (about 50% of the world's adult population) by 2030 **[1]**. There are also worrying increases in the number of adults with obesity who are likely to need medical intervention during their lifetime, with serious implications for health systems. Obesity is a disease and one of the main drivers of noncommunicable chronic diseases (NCDs), including some types of cancer, heart disease, stroke, and type II diabetes **[1,2]**. Overweight and obesity have significant implications for individual and societal health. Body mass index (BMI) values above normal are related to a higher risk of NCDs, such as cardiovascular disease, diabetes, musculoskeletal diseases, and some types of cancer, as well as being associated with higher mortality rates **[3]**.

In this context, melatonin (MEL) therapy and its pharmacological analogues stand out as therapeutic agents for the treatment of various pathologies, mainly obesity, metabolic diseases, and diabetes. Thus, over the last 20 years, solid experimental and some clinical evidence has accumulated on the important role of MEL in the regulation of energy metabolism **[4,5]**.

The sleep-wake cycle is critical for the secretion and physiological variations of several hormones, including MEL **[6]**. Melatonin (N-acetyl-5-methoxytryptamide), an indoleaminergic hormone, is produced mainly by the pineal gland, but also in the gastrointestinal tract, retina, lacrimal glands, skin, erythrocytes, platelets, lymphocytes, and mononuclear cells of the bone marrow, derived from the noradrenergic stimulation of tryptophan and serotonin by α1 and β1 adrenoreceptors in postsynaptic pinealocytes **[7]**.

In this sense, individuals who present with an absence or reduction in MEL production may develop insulin resistance, glucose intolerance, disorders in insulin secretion, dyslipidemia, energy balance disorders, and obesity. Furthermore, the usual daily distribution of metabolism associated with the sleep-wake cycle and the food intake-fasting cycle disappears completely **[8]**.

The daily metabolic cycle characterized by a phase that temporally associates increased insulin sensitivity and increased glucose-stimulated secretion with the large daily food intake, and by another phase that associates insulin resistance, mainly hepatic, and subsequent gluconeogenesis with the sleep or rest period, disappears completely, characterizing a condition where there is a disturbance of circadian rhythmicity, called chronodisruption **[9]**.

Unlike other hormonal axes, MEL secretion is not regulated by feedback and, for this reason, its plasma concentrations do not depend on its production. Pineal gland secretion is controlled by the circadian cycle in the suprachiasmatic nucleus of the hypothalamus and, consequently, promotes peak MEL secretion at night and decreases during the day due to light exposure **[10]**.

MEL has endocrine and paracrine actions and binds to three central and peripheral receptors in various locations in the body **[11]**. The high-affinity receptors MT1 and MT2, or MTNR1A and MTNR1B, belong to the family of membrane-bound receptors with G protein activation by PKC and cyclic guanosine monophosphate (cGMP), respectively. The recently discovered MT3, nuclear receptor of the retinoic acid family (RZR/ROR), has a quinone reductase-type structure with a function that is not yet fully understood **[12]**.

There is a decrease in MEL secretion with aging and the presence of various diseases **[12]**. The sleep pattern undergoes changes, and this has a great impact with advancing age and the development of certain diseases, such as obesity and type 2 diabetes. MEL has been recommended for use in cases of sleep disorders, such as insomnia and jet lag. However, pleiotropic actions of MEL, such as metabolic functions, regulation of obesity and diabetes, can be extremely useful in several diseases **[13]**.

Therefore, a meta-analysis study of melatonin nutritional therapy in the treatment of patients with obesity and meta-inflammation was developed.

Methods

Study Design

This study followed an international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) guidelines. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 08/19/2025. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 08/19/2025.

Research Strategy and Sources

The literature search process was conducted from July to August 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present. The following descriptors (DeCS / MeSH Terms) were used: "Obesity.

Weight loss. Inflammatory processes. Metabolic syndrome. Melatonin", and using the Boolean operator "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by means of the Funnel Plot analysis (Sample size versus Effect size), using Cohen's d test.

Statistical Analysis

Stata 18 and Minitab 21 software were used to process the data resulting from this study. Cohen's t-test was performed to calculate the effect size, and the inverse standard error (sample size) was used to determine if there was a risk of bias through analysis of the graphical symmetry of the studies in the Funnel Plot. A Forest-Plot was also developed to present the results of melatonin's action on weight loss (kg) through Odds Ratio (OR) analysis, with $p<0.05$ significant. The Heterogeneity Test (Chi-Square Test – X^2) was also performed on the results of the studies, adopting $X^2>50\%$ with homogeneous results between studies, and $p<0.05$ without a statistically significant difference, in the 95% CI. The analyses followed Pearson's Chi-square test, with $p<0.05$ indicating statistical significance of association, with a 95% confidence interval (CI). Binary and predictive logistic regression analysis was also performed, with $p<0.05$ being significant.

Main Clinical Findings – Meta-Analysis

Summary of Findings

A total of 121 articles were submitted to eligibility analysis, with 18 final studies selected to compose the results of this meta-analysis. The listed studies presented medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with $X^2=96.8\%>50\%$. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 20 studies with a high risk of bias and 24 studies that did not meet the GRADE and AMSTAR-2 criteria.

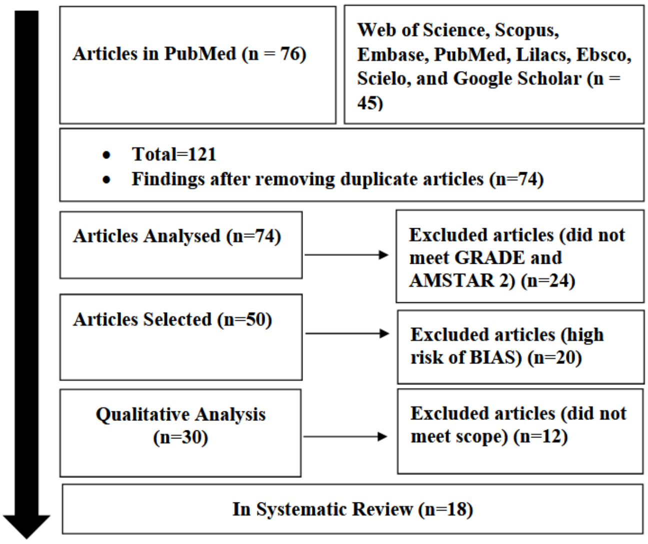

Figure 1. Selection of articles. Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). The precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are presented in the upper region.

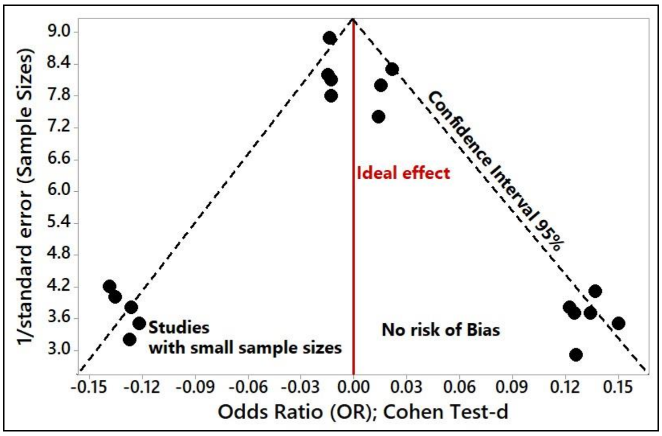

Figure 2. The symmetrical funnel plot does not suggest a risk of bias between the small sample size studies that are shown at the bottom of the graph. High confidence and high recommendation studies are shown above the graph. N=18 studies. Source: Own Authorship.

The results of eighteen clinical studies, with 4,678 participants, were analyzed. The results were significant, indicating that melatonin imbalance can lead to metabolic disorders and circadian rhythm disturbances, $p < 0.05$ (R2 = 96.8%). In addition, the studies demonstrated improvement in metabolic disorders, glycemic homeostasis, weight loss (> 3.0 kg/month), reduction of the inflammatory process, and improved sleep after supplementation with 5.0 mg (±5.0) melatonin, showing a significant probability of weight loss, with an Odds Ratio (OR) equal to 3.28 (2.31 to 4.59; 95% CI), after logistic regression analysis, with $p<0.05$, as shown in Figure 3. However, the best concentration to be used in humans, especially in the long term, is still unknown.

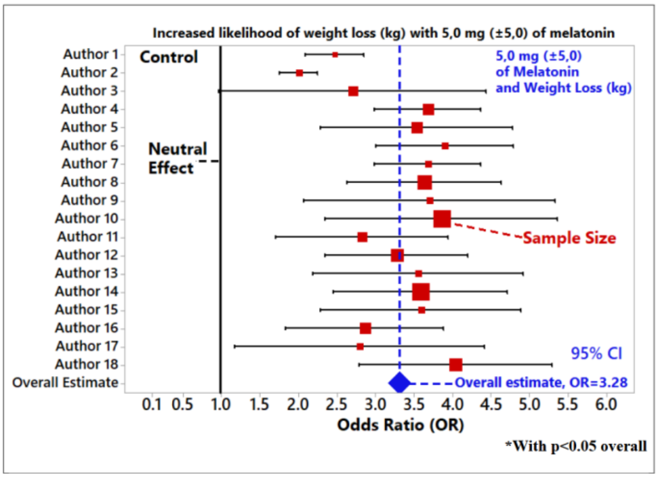

Figure 3. Forest-Plot graph showing the increased probability of weight loss and improvement in comorbidities with the use of 5.0 mg of melatonin, with 95% CI. Source: Own Authorship.

MEL is a well-known and effective antioxidant, as it is both a proficient scavenger of direct free radicals and an activator of a series of elimination mechanisms, such as stimulating the transcription and activity of antioxidant enzymes and binding to transition metals that inhibit the formation of hydroxyls. In addition, MEL protects lipids, proteins, and DNA against oxidative damage, being highly concentrated in mitochondria **[4]**.

In this context, the antioxidant properties of MEL are of crucial importance for mitochondrial functions, playing critical roles in mitochondrial function beyond antioxidant protection, such as regulating the activities of respiratory complexes I and IV and protecting mitochondrial DNA against chromosomal/chromatid alterations and mutations **[5,6]**. Thus, some of the aforementioned effects are generally a consequence of the direct MEL-protein interaction. It is also noteworthy that MEL plays a role in regulating the ubiquitin-proteasome system, which ultimately controls protein degradation **[7]**. Furthermore, MEL has been reported to inhibit Ca2+/calmodulin-dependent protein kinase II activity and autophosphorylation through a direct interaction with Ca2+-activated calmodulin, acting as an antagonist. It has also been suggested that MEL influences the expression of circadian rhythm genes **[8]**.

MEL MT1 and MT2 receptors, formerly termed MEL1a and MEL1b, are high-affinity specific G protein-coupled receptors encoded by the MTNR1A and MTNR1B genes, which have been found in various areas of the CNS, including the SCN, mediobasal hypothalamus, thalamus, temporal, parietal and frontal cortex, hippocampus, preoptic basal ganglia, area postrema, retina, cerebellum and pars tuberalis region, as well as in adipose tissue, kidney, pancreas islets, parotid glands, adrenal glands, liver, bone, skin, reproductive tract, immune cells and cardiovascular system **[9-11]**.

Despite all these findings on the physiological functions of MEL, the metabolic pathways involved in human sleep still need to be investigated using a metabolomics approach. Thus, a study performed targeted liquid chromatography (LC)/MS metabolomics to examine the effect of acute sleep deprivation on plasma metabolite rhythms. Twelve young, healthy male subjects remained under controlled laboratory conditions regarding ambient light, sleep, meals, and posture during a 24-hour sleep/wake cycle, followed by 24 hours of wakefulness. Two-hour plasma samples collected during the 48-hour period were analyzed by LC/MS. Principal component analysis revealed a clear time-of-day variation with a significant cosine fit during the sleep/wake cycle and during 24 hours of wakefulness in both untargeted and targeted analyses. Of the 171 metabolites quantified, diurnal rhythms were observed in most (n = 109), with 78 of them maintaining their rhythmicity during 24 hours of wakefulness, most with reduced amplitude (n = 66). During sleep deprivation, 27 metabolites (tryptophan, serotonin, taurine, 8 acylcarnitines, 13 glycerophospholipids, and 3 sphingolipids) exhibited significantly increased levels compared to sleep. The increased levels of serotonin, tryptophan, and taurine may explain the antidepressant effect of acute sleep deprivation **[8]**.

Another study aimed to analyze the importance of chronobiology, represented by MEL and cryptochrome 2 (CRY2), in the development of metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM). Thus, plasma levels of MEL and CRY2 were compared, and the two biomarkers were correlated with adiposity, atherogenicity, and hematology indices **[8]**. In a cross-sectional study, 28 normoglycemic lean individuals (controls), 29 normoglycemic individuals with MS, and 30 individuals with MS (pre-diabetic/diabetic) were recruited. As a result, MEL (pg/mL) significantly increased in the MS group with $p<0.05$, while CRY2 levels (ng/mL) were markedly higher in both MS groups (non-diabetic and pre-diabetic/diabetic) (all with p-value <0.001). A reciprocal relationship was observed with MEL-CRY2 in the SM (non-diabetic) group (p-value = 0.003). It is important to note that, in the total study population, MEL and CRY2 correlated proportionally with each of the following items: plasma atherogenic index (PAI), waist circumference (WC), and systolic blood pressure (SBP) (all with p-value <0.05 for MT and CRY2, respectively). While MEL correlated inversely with HDL-C (p-value <0.05). Furthermore, CRY2 correlated directly with each of the following: diastolic blood pressure, total cholesterol, LDL-C, hip circumference, body adiposity index, weight-for-height ratio, mean platelet volume, and platelet/lymphocyte ratio (p-value <0.05). Therefore, these findings prove that both metabolic risk biomarkers can be prognostic tools and pharmacotherapeutic targets to slow down the accelerated nature of T2DM **[9]**.

Despite the importance of the genetic role in energy metabolism, environmental variables have a strong impact on the global obesity epidemic. Although greater emphasis is placed on poor diet and physical inactivity, other causes have been related, such as sleep deprivation **[12]**. In recent years, there has been a significant reduction in sleep hours, and recent epidemiological studies show the relationship between short sleep hours and increased body mass index. Several studies point to a higher risk of developing obesity in people who sleep less than six hours a day **[13-15]**.

Studies suggest a direct and an indirect action of MEL in important stages of the adipocyte biological cycle, such as lipolysis, lipogenesis, adipocyte differentiation, and uptake of free fatty acids and insulin action in these adipose cells through MT1 and MT2 receptors **[14,15]**. Although the main stimulus for the noradrenergic pineal gland is activated by the absence of light, other peptides can modulate MEL secretion, such as vasoactive intestinal polypeptide, neuropeptide Y, glutamate, angiotensin, insulin, and leptin, showing once again the important relationship of this hormone with other substances essential to metabolism and body homeostasis **[16]**.

In this context, the increase in appetite after sleep deprivation in people who work the night shift is noteworthy **[17]**. The hormonal changes that occur during sleep deprivation may explain the increased caloric intake and decreased leptin (anorexic hormone) and increased ghrelin and peptide YY (orexigenic hormones). In addition, reduced sleep time seems to alter the preference for high-calorie foods and reduce energy expenditure. Seasonal changes are also related to sleep, MEL levels, and weight gain **[18]**.

In addition to the way MEL regulates body weight, there is another, more direct way, which occurs through its role in regulating energy balance. Thus, all the energy ingested through food is used or stored in energy reserves for future use. There is solid experimental evidence showing that MEL acts by regulating each of the stages of energy balance **[17,18]**.

MEL is a hormone that mainly regulates food intake through central action, regulating the production and secretion of insulin, glucagon, and cortisol, thus organizing the flow of energy reserves to and from stores, and also increases energy expenditure, increasing the mass and activity of brown adipose tissue and increasing the browning of white adipose tissue. It can therefore be seen as another anti-obesogenic hormonal factor **[19]**.

As a chronobiotic and cytoprotective agent, MEL occupies a special place in the prevention and treatment of metabolic syndrome. Since mitochondrial activity is modulated by the availability of energy in cells, the disruption of key metabolic regulators in MS affects not only mitochondrial activity but also their dynamics and turnover. Thus, MEL levels are reduced in diseases associated with insulin resistance, such as metabolic syndrome. Furthermore, MEL improves sleep efficiency and has antioxidant and anti-inflammatory properties, partly due to its role as a metabolic regulator and mitochondrial protector **[11]**.

With the increase in obesity, there is consequently an increase in complications such as T2DM **[16]**. MEL plays an important role in insulin signaling and its lack has diabetogenic effects **[17-19]**. Epidemiological studies also show a link between sleep deprivation, insulin resistance and T2DM. A cohort analysis of the Nurses' Health Study showed that lower levels of 6-sulfatoxymelatonin, a urinary metabolite of MEL, are related to the incidence of T2DM, and low secretion of this hormone is a strong independent risk factor for the development of this disease. The same urinary metabolite is also decreased in diabetic patients with diabetic retinopathy compared to patients without this microvascular complication **[16]**.

MEL affects the insulin secretory activity of pancreatic β cells, hepatic glucose metabolism, and insulin sensitivity. Individuals with T2DM have lower serum levels of MEL at night and a higher risk of sleep disorders compared to healthy individuals. In addition, reduced levels of MEL and genetic mutations and/or polymorphisms of MEL receptors are associated with an increased risk of developing T2DM. Many studies have shown the importance of melatonin in various diseases, mainly in obesity, T2DM, and metabolic syndrome. Studies in humans have shown that the use of melatonin is simple, safe, and has no side effects. Despite this, intervention studies using this hormone in obese or diabetic patients have not yet reached a consensus on supplementation **[19,20]**.

Finally, MEL is an important participant in the regulation of energy metabolism, including body weight, insulin sensitivity, and glucose tolerance **[20]**. In this sense, MEL regulates energy metabolism, acting at all stages of energy balance, including energy intake, energy flow to and from stores, and energy expenditure. In addition, MEL, through its chronobiotic and seasonal effects, synchronizes energy metabolism requirements with daily and annual rhythms **[21]**.

Limitations

Significant gaps remain in the research, including inconsistent methodologies, small sample sizes, and limited data on long-term effects, requiring more robust clinical trials. Individualized recommendations and cautious interpretation of results are essential, especially due to variability in results based on study designs and populations.

Conclusion

It was concluded that melatonin supplementation with an average of 5.0 mg was responsible for a significant reduction in body weight and comorbidities in patients with obesity and meta-inflammation. Melatonin also regulates food intake by regulating the production and secretion of insulin, glucagon, and cortisol, as well as playing an important role in insulin signaling, and its deficiency has diabetogenic effects.

CRediT

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The authors declare no conflict of interest.

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Application of Artificial Intelligence (AI)

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