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REVIEW ARTICLE

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Control and treatment of obesity comorbidities by melatonin nutrological therapy: a systematic review

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Abstract

Introduction: There are more than 2.2 billion overweight and obese people worldwide. Sleep imbalance and the resulting reduction in melatonin (MEL) concentrations in the human body have a significant impact on health, particularly the development of obesity and comorbidities. **Objective:** This was to conduct a systematic review of the main approaches and clinical studies on melatonin regulation in the control and treatment of obesity and its comorbidities. **Methods:** The PRISMA rules for systematic review were followed. This study included review articles, systematic reviews/meta-analyses, prospective studies, retrospective studies, and randomized, double-blind, placebo-controlled trials in humans. **Results and Conclusion:** 27 of the 30 studies were selected to compose the results of this systematic review. Most studies presented homogeneity in their results, with X^2=83.3%>50%. It was concluded that melatonin is an important participant in the regulation of energy metabolism, including body weight, insulin sensitivity, and glucose tolerance. Randomized placebo-controlled clinical studies have shown that daily melatonin consumption can be effective in controlling blood pressure, including systemic blood pressure, mean arterial pressure and pulse pressure, and reduces anthropometric indices of obesity in patients, as it increases the mass and activity of brown adipose tissue, functioning as an anti-obesogenic hormone. Melatonin can regulate adipose tissue and adipokines, such as adipocyte lipolysis and fat deposition. Furthermore, melatonin can interact with intracellular molecules, acting as an effective antioxidant. Several studies have indicated a higher risk of developing obesity in people who sleep less than six hours a day. Hormonal changes that occur during sleep deprivation may explain the increase in caloric intake and decrease in leptin, increase in ghrelin and peptide YY. Melatonin also regulates food intake by controlling the production and secretion of insulin, glucagon, and cortisol. Epidemiological studies have shown a link between sleep deprivation, insulin resistance, and T2DM.

Keywords: Obesity. Melatonin. Comorbidities.

Introduction

In the context of chronic noncommunicable diseases, there are more than 2.2 billion people worldwide who are overweight or obese, with approximately 40% of American adults and 20% of young people being obese **[1]**. Brazil is estimated to have an additional 21.0 million people by 2030 **[2]**. Studies indicate that a reduction of approximately 10.0% in weight also favors the reduction of type 2 diabetes mellitus (T2DM) **[3-5]**.

In this context, clinical studies have advanced our understanding of the physiological role of melatonin (N-Acetyl-5-Methoxytryptamine; MEL) and its pharmacological analogues as therapeutic agents for the treatment of various pathologies, primarily obesity, metabolic diseases, and diabetes. Thus, over the past 20 years, solid experimental and some clinical evidence have accumulated on the important role of MEL in regulating energy metabolism **[3,4]**.

In this context, the sleep-wake cycle is critical for

the secretion and physiological variations of several hormones, including MEL [5]. MEL is a hormone produced primarily by the pineal gland, but also in the gastrointestinal tract, retina, lacrimal glands, skin, erythrocytes, platelets, lymphocytes, and bone marrow mononuclear cells, derived from the noradrenergic stimulation of tryptophan and serotonin by α1 and β1 adrenoreceptors in postsynaptic pinealocytes [6].

Individuals with absent or reduced MEL production may develop insulin resistance, glucose intolerance, insulin secretion disorders, dyslipidemia, energy balance disorders, and obesity. Furthermore, the usual daily metabolic distribution associated with the sleep-wake cycle and the food intake-fasting cycle completely disappears [7]. Thus, the daily metabolic cycle, characterized by a phase that temporally associates increased insulin sensitivity and increased insulin secretion stimulated by glucose from the daily diet, and another phase that associates insulin resistance, primarily hepatic, and subsequent gluconeogenesis with sleep or rest, completely disappears, characterizing a situation where there is a disruption of circadian rhythm (chronodisruption) [8].

Unlike other hormonal axes, MEL secretion is not regulated by feedback and, therefore, 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 is decreased during the day by light exposure [9]. In addition, MEL has endocrine and paracrine actions and binds to three receptors, central and peripheral, in various locations throughout the body [10]. The high-affinity receptors MT1 and MT2, or MTNR1A and MTNR1B, belong to the family of membrane-bound receptors with Gprotein activation by PKC and reduced cyclic GMP monophosphate (cGMP), respectively. MT3, a recently discovered nuclear receptor of the retinoic acid (RZR/ROR) family, has a quinone reductase-like structure, with its function not yet fully understood [11].

Also, MEL secretion decreases with aging and the presence of various diseases [11]. Sleep patterns change, and this has a significant impact with advancing age and the development of certain diseases such as obesity and T2DM. MEL has been recommended for use in cases of sleep disorders such as insomnia and jet lag. However, MEL's pleiotropic actions, such as metabolic functions, regulation of obesity, and diabetes, may be extremely useful in various diseases [12].

Therefore, the present study developed a systematic review of the main approaches and clinical studies on melatonin regulation in inflammatory processes and type 2 diabetes mellitus in patients with obesity.

Methods

Study Design

This study followed the 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: April 17, 2025. The AMSTAR 2 (Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: April 17, 2025.

Search Strategy and Search Sources

The search strategies for this systematic review were based on the keywords (DeCS/MeSH Terms): *"Obesity. Melatonin. Comorbidities."* The search was conducted from April to May 2025 in the Scopus, Embase, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Boolean operators "OR," "AND," and the "NOT" operator was used to target scientific articles of interest.

Study Quality and Risk of Bias

Study quality was based on the GRADE instrument, prioritizing studies with scientifically rigorous methodology. Quality was classified as high, moderate, low, or very low based on risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent articles were systematic reviews or meta-analyses of randomized controlled trials, followed by randomized clinical trials. Low-quality evidence was attributed to case reports, editorials, and brief communications. Risk of bias was analyzed according to the Cochrane instrument by analyzing the funnel plot (sample size versus effect size) using Cohen's d test.

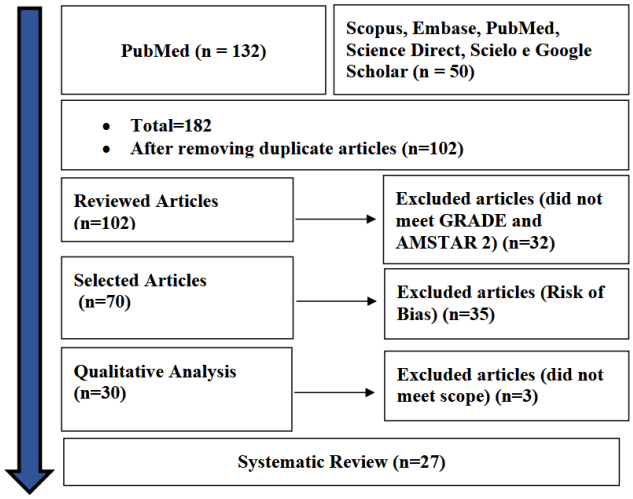
Results and Discussion

Summary of Findings

A total of 182 articles were found and submitted for eligibility analysis. After removing duplicate articles, 102 studies were selected. Using the Cochrane risk of bias tool, 35 studies with a high risk of bias, 32 studies that did not meet the GRADE and AMSTAR 2 criteria, and 3 studies that did not meet the scope of this study were excluded. Of the 30 references included in this study, 27 correspond to scientific articles that comprised the results of this systematic review. The listed studies were of medium to high quality (Figure 1), considering the level of scientific evidence from studies such as meta-analysis, consensus, randomized

clinical, prospective, and observational studies. Biases did not compromise the scientific basis of the studies. According to the GRADE tool, most studies presented homogeneity in their results, with X^2=83.3%>50%.

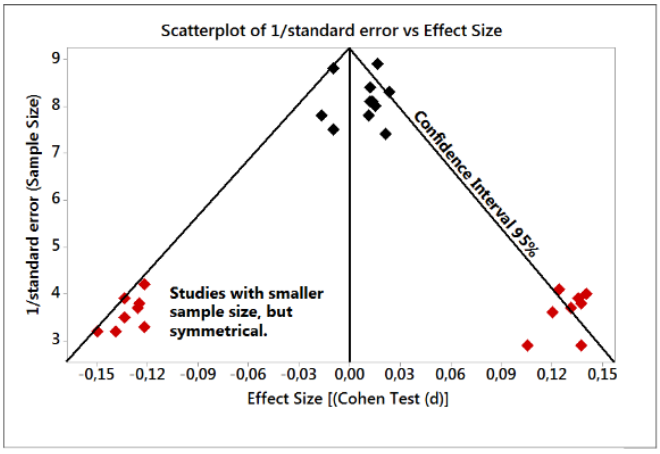
Figure 1. Article selection process.



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 d test. Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph displayed symmetrical behavior, suggesting no significant risk of bias, either among studies with small sample sizes (lower precision), shown at the bottom of the graph in red, or among studies with large sample sizes, shown at the top in black.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes, shown at the bottom of the graph (studies in red, n=16 studies). High-confidence and high-recommendation studies are shown above the graph (studies in black, n=11 studies).



Source: Own authorship.

Melatonin and Meta-inflammatory Processes in Obesity

Melatonin supplementation has received considerable attention for its potential health benefits. Recent studies highlight the promising antioxidant, anti-inflammatory, and immunomodulatory properties of melatonin, particularly in improving sleep quality and treating specific neurodegenerative diseases. Evidence supports its role in reducing anxiety in preoperative settings and enhancing recovery in athletes under certain conditions. However, findings on the role of melatonin in obesity, glycemic control, and gut microbiome regulation remain inconsistent and are influenced by external factors such as diet and exercise **[1]**.

In endocrine physiology, due to its amphiphilic nature, MEL is capable of crossing cells, organelles, and nuclear membranes and directly interacting with intracellular molecules in so-called non-receptor-mediated actions **[3]**. MEL is an effective antioxidant, protecting lipids, proteins, and DNA against oxidative damage **[4-7]**.

In this sense, a cross-sectional case-control clinical study analyzed 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. Twenty-eight normoglycemic lean individuals (controls), 29 normoglycemic individuals with MS, and 30 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 prediabetic/diabetic) (all $p<0.001$). A reciprocal relationship with MEL-CRY2 was observed in the MetS (non-diabetic) group ($p=0.003$). It is important to note that, in the total study population, MEL and CRY2 correlated proportionally with each of the following plasma atherogenicity index (PAI), waist circumference (WC), and systolic blood pressure (SBP) (all $p<0.05$) for MetS and CRY2, respectively. MEL correlated inversely with HDL-C ($p<0.05$). 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-to-lymphocyte ratio ($p<0.05$) **[8]**.

In this context, there has been a significant reduction in sleep hours in recent years, and recent epidemiological studies have shown the relationship between short sleep hours and increased body mass index. Several studies point to a higher risk of obesity

in people who sleep less than six hours per day **[12-14]**. Studies suggest both a direct and indirect action of MEL on important stages of the adipocyte biological cycle, such as lipolysis, lipogenesis, adipocyte differentiation, and free fatty acid uptake, as well as insulin action on these adipocyte cells through MT1 and MT2 receptors **[13,14]**.

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, demonstrating once again the important relationship of this hormone with other substances essential to metabolism and body homeostasis **[15]**.

Based on this, the increase in appetite after sleep deprivation in people who work the night shift is notable **[16]**. The hormonal changes that occur during sleep deprivation may explain the increased caloric intake and decreased leptin (anorectic hormone) and increased ghrelin and peptide YY (orexigenic hormones). Furthermore, reduced sleep time appears to alter the preference for calorie-rich foods and reduce energy expenditure. Seasonal changes are also related to sleep, MEL levels, and weight gain. Furthermore, there is solid experimental evidence showing that MEL acts by regulating each of the stages of energy balance **[17]**.

In this regard, MEL is a hormone that can regulate food intake, regulating the production and secretion of insulin, glucagon, and cortisol, regulating the flow of energy reserves, increasing the mass and activity of brown adipose tissue, and increasing the browning of white adipose tissue. Thus, MEL functions as an anti-obesogenic hormonal factor **[18]**.

This is extremely important, as obesity promotes an increase in complications such as T2DM **[15]**. MEL plays an important role in insulin signaling, and its deficiency has diabetogenic effects **[16-18]**. Epidemiological studies also show a link between sleep deprivation, insulin resistance, and T2DM **[15]**. Furthermore, MEL affects the insulin-secreting activity of pancreatic β cells, hepatic glucose metabolism, and insulin sensitivity. Furthermore, reduced MEL levels and genetic mutations and/or polymorphisms of MEL receptors are associated with an increased risk of developing T2DM.

In addition, obesity is known to be characterized by severe dysfunction of white adipose tissue (WAT), with alterations in endocrine function **[19]**. WAT acts as an energy store, and brown adipose tissue (BAT) **[20]** acts as an energy consumer. Both BAT and beige adipose tissue formed by WAT browning contain abundant mitochondria and uncoupling protein (UCP) 1, which benefits weight loss and energy burning **[21]**. In this tissue system, MEL has been reported to regulate adipose tissue and adipokines, such as adipocyte lipolysis, fat deposition, BAT growth, beige adipogenesis, and WAT browning **[22,23]**.

MEL can induce lipolysis and upregulate the expression of lipolytic genes and enzymes via MT2, including hormone-sensitive lipase (HSL), adipocyte triglyceride lipase (ATGL), and perilipin 1 (PLIN1) **[24,25]**. A recent single-cell RNA sequencing study of preadipocytes showed that MEL induced preadipocyte heterogeneity, producing a G0S2-cell subtype, which is beneficial for promoting lipolysis and inhibiting adipogenesis. MEL plays this role by downregulating G0S2 in the G0S2-cell subtype, thereby leading to the activation of adipose triglyceride lipase, or by upregulating fatty acid-binding protein 4 (FABP4) in the G0S2-cell cluster, as well as by inhibiting PPARγ, further reducing adipogenesis **[26]**. Thus, MEL stimulates BAT growth, improves BAT quality and activity, improves mitochondrial function and activity, and increases UCP1 expression, as well as decreasing oxidative and nitrosative stress **[27]**.

A randomized, placebo-controlled clinical trial conducted by authors Mohammadi et al. (2021) **[28]** analyzed the effects of melatonin supplementation on body weight, body mass index (BMI), waist circumference (WC), and body fat mass percentage (BFMP) in overweight or obese individuals. A total of 38 overweight or class I obese adults were recruited for the study (8 men and 30 women). Participants received a weight-loss diet and were then randomly allocated to a melatonin or a placebo group. Participants received a 3.0mg melatonin tablet or placebo daily for 12 weeks. According to the results, a significant reduction in body weight, WC, and BMI was found in both groups ($p=0.001$). However, in the last six weeks, significant reductions in these parameters were observed only in the melatonin group ($p=0.01$), with $p<0.05$ significant. The BFMP of participants in the melatonin group showed a significant reduction at the end of the study compared to baseline measurements ($p=0.008$).

Finally, the authors Bazyar et al. (2021) **[29]** investigated through a randomized, placebo-controlled, double-blind clinical study the effects of MEL supplementation on some cardiovascular disease risk factors and anthropometric indices in patients with T2DM. A total of 50 patients with T2DM were randomly allocated to intervention and control groups who received two melatonin tablets (3mg) or a placebo (250mg) once daily for 8 weeks. Systolic blood pressure (SBP), mean arterial pressure (MAP), pulse pressure (PP), plasma atherogenic index (AIP), weight,

BMI, waist and hip circumference (WC, HC), a body shape index (BSI), abdominal volume index (AVI), body adiposity index (BAI), lipid accumulation product (LAP), conicity index, and waist-to-height ratio (WHtR) were assessed in all patients pre- and post-intervention. The results showed that melatonin supplementation for 8 weeks significantly decreased the mean levels of SBP, MAP, PP, weight, BMI, WC, WC, BAI, AVI, conicity index, and WHR post-intervention, with a significant p-value of $p<0.05$. Furthermore, the median changes in SBP, MAP, PP, weight, BMI, WC, BAI, AVI, and conicity index were significantly lower in the intervention group compared to the control group ($p<0.05$). A significant increase ($p<0.001$) was observed in the mean levels of BSI in the intervention group. The changes in BSI were significantly greater in the intervention group compared to the control group ($p<0.001$).

Limitations

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

Conclusion

It was concluded that melatonin is a hormone that regulates energy metabolism, including body weight, insulin sensitivity, and glucose tolerance. Randomized placebo-controlled clinical trials have shown that daily melatonin consumption can be effective in controlling blood pressure, including systemic blood pressure, mean arterial pressure, and pulse pressure, and reduces anthropometric indices of obesity in patients, as it increases the mass and activity of brown adipose tissue, acting as an anti-obesogenic hormone. Melatonin can regulate adipose tissue and adipokines, such as adipocyte lipolysis and fat deposition. Furthermore, melatonin is capable of interacting with intracellular molecules, acting as an effective antioxidant. Several studies have indicated a higher risk of developing obesity in people who sleep less than six hours a day. The hormonal changes that occur during sleep deprivation may explain the increased caloric intake and decreased leptin, increased ghrelin, and peptide YY. Melatonin also regulates food intake, regulating the production and secretion of insulin, glucagon, and cortisol. Some epidemiological studies have shown a link between sleep deprivation, insulin resistance, and T2DM.

CRediT

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Informed Consent

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Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate[@].

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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