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REVIEW ARTICLE

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Clinical results of the functions of melatonin in the mitigation of comorbidities of obesity and type 2 diabetes mellitus: a systematic review

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Abstract

Introduction: In the scenario of chronic non-communicable diseases, there are more than 2.2 billion overweight and obese people in the world. Brazil has an estimated population of more than 20.0 million people in 2025. Studies show that a reduction of around 10.0% in weight also favors the reduction of type 2 diabetes mellitus (T2DM). The imbalance in sleep patterns and the consequent decrease of melatonin (MEL) concentrations in the human body have a major impact on health with the development, mainly of obesity and T2DM. **Objective:** It was to present the main clinical results of the functions of melatonin in mitigating the comorbidities of obesity and type 2 diabetes mellitus. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from May to June 2024 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 182 articles were found. A total of 35 articles were evaluated in full and 28 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 35 studies with a high risk of bias and 32 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=77.8%>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 mass and activity of brown adipose tissue, functioning as an antiobesogenic 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 pointed to a greater 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 increase in caloric intake and decrease in leptin, increase in ghrelin and peptide YY. Melatonin also regulates food intake by regulating the production and secretion of insulin, glucagon, and cortisol. Epidemiological studies have shown a link between sleep deprivation, insulin resistance, and T2DM.

Keywords: Obesity. Type 2 diabetes mellitus. Melatonin. Comorbidities. Energy metabolism.

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 over 20 million people by 2025 **[2]**. Studies indicate that a weight reduction of approximately 10.0% also helps reduce type 2 diabetes mellitus (T2DM) **[3-5]**.

In this context, clinical studies have advanced on the physiological role of melatonin [MEL (N-acetyl-5-methoxytryptamide)] and its pharmacological analogs 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]**.

Consequently, individuals with absent or reduced MEL production may develop insulin resistance, glucose intolerance, disorders of insulin secretion, 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, is 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]**.

Furthermore, 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, and regulation of obesity, and diabetes may be extremely useful in various diseases **[12]**.

Therefore, the present study aimed to present the main clinical results of the functions of melatonin in mitigating the comorbidities of obesity and type 2 diabetes mellitus.

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: June 17, 2024. The AMSTAR 2

(Assessing the Methodological Quality of Systematic Reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: June 17, 2024.

Search Strategy and Search Sources

The search strategies for this systematic review were based on the health sciences descriptors (DeCS/MeSH Terms): *"Obesity. Type 2 diabetes mellitus. Melatonin. Comorbidities. Energy metabolism"* The search was conducted from May to June 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Boolean terms "OR," "AND," and the operator "NOT" were used to target scientific articles of interest.

Study Quality and Risk of Bias

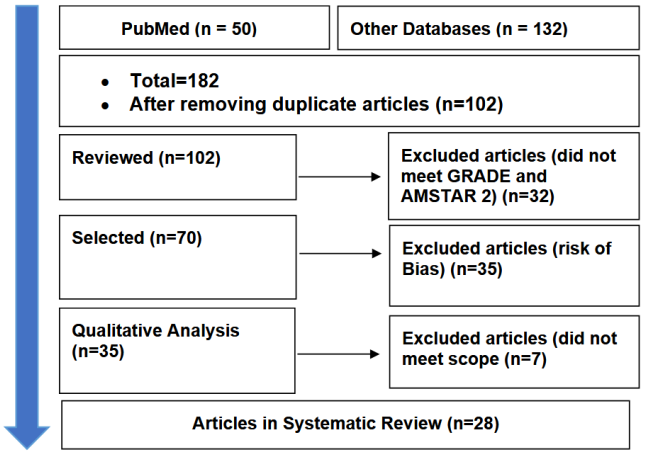
Study quality was based on the GRADE instrument, prioritizing studies with scientifically rigorous methodology. Quality was classified as high, moderate, low, or very low based on the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most prominent articles were systematic 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. The 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.

Literary Review and Results

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 GRADE and AMSTAR 2 criteria, and 8 studies with a low risk of bias were excluded. Of the 30 references included in this study, 28 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 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 tool, most studies presented homogeneity in their results, with X^2=77.8%>50%.

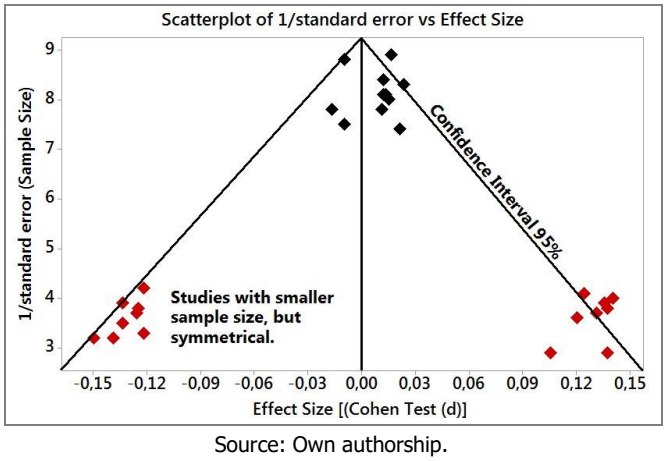
Figure 1. Flowchart showing the article selection process.



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 exhibited 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). High-confidence and highly recommended studies are shown above the graph (studies in black).



Source: Own authorship.

Melatonin, Obesity, and Type II Diabetes - Key Clinical Studies

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 regard, 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 (MetS) and type 2 diabetes mellitus (T2DM). Plasma levels of MEL and CRY2 were compared and the two biomarkers were correlated with adiposity, atherogenicity, and hematologic indices. Twenty-eight lean normoglycemic individuals (controls), 29 individuals with normoglycemic MetS, and 30 individuals with MetS (pre-diabetic/diabetic) were recruited. As a result, MEL (pg/mL) was significantly increased in value in the MetS group with $p<0.05$, while CRY2 (ng/mL) levels were markedly higher in both MetS groups (non-diabetic and pre-diabetic/diabetic) (all $p<0.001$). A reciprocal relationship with MELCRY2 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 proportionally correlated with each of the following: plasma atherogenicity index (PAI), waist circumference (WC), and systolic blood pressure (SBP) (all $p<0.05$) for MT and CRY2, respectively). While MEL inversely correlated 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, in recent years there has been a significant reduction in sleep hours, 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 developing 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 the MT1 and MT2 receptors **[13,14]**.

Although the primary stimulus for the noradrenergic pineal gland is activation 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 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 to regulate each of the stages of energy balance **[17]**.

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

This is extremely important, as obesity promotes the 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.

Additionally, 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 the beige adipose tissue formed by WAT browning contain abundant mitochondria and uncoupling protein (UCP) 1, which benefit 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]**.

Furthermore, 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 study with single-cell RNA sequencing of preadipocytes showed that MEL induced preadipocyte heterogeneity, producing a G0S2- cell subtype, which is of great benefit for promoting lipolysis and inhibiting adipogenesis. MEL plays this role by downregulating G0S2 in the G0S2- cell subtype and thus 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 leading to the inhibition of 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 decreases oxidative and nitrosative stress [27].

A randomized, placebo-controlled clinical trial conducted by 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 obese adults (8 men and 30 women) were recruited for the study. Participants were prescribed a weight-loss diet and then randomly assigned to a melatonin or placebo group. Participants received either a 3.0 mg melatonin tablet or a placebo daily for 12 weeks. According to the results, a significant reduction in body weight, WC, and BMI was found in participants 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 the initial measurements ($p=0.008$).

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 into intervention and control groups who received two melatonin tablets (3mg) or 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), 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 WHtR post-intervention, with a significant p-value of $p<0.05$. Furthermore, the median changes in SBP, MAP, PP, weight, BMI, WC, 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 ($p<0.001$).

Finally, night shift work is associated with sleep disturbances, obesity, and cardiometabolic diseases. Disruption of the circadian clock system has been suggested to be an independent cause of T2DM and cardiovascular disease. Authors Hannemann et al. (2024) [30] determined to improve the alignment of circadian timing with social and environmental factors with melatonin administration in a prospective randomized, placebo-controlled study. 2 mg of sustained-release melatonin versus placebo was administered on glucose tolerance, indices of insulin resistance, sleep quality, circadian profiles of plasma melatonin and cortisol, and daytime blood pressure in 24 rotating night shift workers during 12 weeks of treatment followed by 12 weeks of washout. In a novel design, the time of melatonin administration (evening or morning) depended on the shift schedule. The baseline profiles of night shift workers (NS) were also compared with 12 healthy controls working outside of the night shift (NNS). Significantly impaired insulin resistance indices were observed at baseline in NS versus NNS ($p < 0.05$), but there were no differences in oral glucose tolerance tests or diurnal melatonin, cortisol, or blood pressure profiles. Twelve weeks of melatonin treatment did not significantly improve insulin resistance, nor did it significantly affect daytime blood pressure or melatonin and cortisol profiles. Melatonin administration, however, resulted in a significant improvement in sleep quality, which was significantly impaired in NS versus NNS at baseline ($p < 0.001$).

Conclusion

It was concluded that melatonin is concluded to be an important player in the regulation of 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. 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. Epidemiological studies have shown a link between sleep deprivation, insulin resistance, and T2DM.

CRediT

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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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