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REVIEW ARTICLE

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Effects of melatonin in the prevention of cardiovascular diseases: a systematic review

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Abstract

Introduction: Obesity represents a multifactorial disease that causes major public health problems. There are about 2.0 billion overweight and obese people in the world, represented by 39.6% of adults. Melatonin may provide cardioprotection at low pharmacological doses. Melatonin's ability to improve cardiovascular function and its hypotensive effect because of its direct and receptor-dependent antioxidant actions suggest that melatonin may have some beneficial effects in controlling diabetic vascular complications. **Objective:** It was to carry out a systematic review of the main effects of melatonin in the treatment of obesity and diabetes mellitus, as well as in the prevention of cardiovascular diseases. **Methods:** The present study followed a concise systematic review model (PRISMA). The literary search process was carried out from April to May 2023 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles until 2023. The low quality of evidence was attributed to case reports, editorials, and short communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 168 studies were found for eligibility analysis, and so 46 of a total of 68 studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2 =90.4%>50%. The Funnel Plot showed a symmetrical behavior, not suggesting a significant risk of bias in studies with smaller sample sizes. It was concluded that melatonin can reduce body weight and fat mass and regulate energy expenditure, glucose/lipid metabolism, and insulin secretion; therefore, it can play an effective role in weight management. There is a growing consensus that the antioxidant and anti-inflammatory properties of melatonin are of great importance in preserving the body's function and homeostasis. In adulthood, disturbances in melatonin production negatively impact the progression of cardiovascular risk factors and promote cardiovascular and neurodegenerative diseases. The consumption of melatonin supplements can be effective in controlling blood pressure and anthropometric indices (as predictors of obesity) in patients with T2DM. Furthermore, melatonin has significant effects on ischemia-reperfusion injury, myocardial injury, pulmonary hypertension, hypertension, vascular diseases, valvular heart diseases, and lipid metabolism. As an inexpensive and well-tolerated drug, melatonin could be a new therapeutic option for cardiovascular diseases.

Keywords: Melatonin. Obesity. Diabetes. Cardiovascular diseases.

Introduction

Obesity represents a multifactorial disease that causes major public health problems **[1]**. There are about 2.0 billion overweight and obese people in the world, represented by 39.6% of adults **[1]**. Brazil ranks fifth, with around 18 million and the prospect of reaching 70 million individuals with obesity **[2]**. Studies indicate that a 5% to 10% reduction in weight also favors the reduction of type 2 diabetes mellitus (T2DM), as well as cardiovascular diseases **[3]**. About 415 million people live with diabetes in the world, corresponding to 1 in every 11 individuals of the adult population, with a perspective of 642 million in 20 years **[3]**.

In this context, research has advanced on the physiological role of melatonin (Nacetyl-5-methoxytryptamide) and its pharmacological analogs as therapeutic agents for the treatment of various diseases, mainly obesity, metabolic diseases, and diabetes. Thus, there is solid experimental and clinical evidence accumulated over the last 20 years about the important role of melatonin in the regulation of energy metabolism **[3-6]**.

The sleep/wake cycle is critical for the secretion and physiological variations of several hormones, including melatonin **[5-9]**. Melatonin is a hormone produced mainly by the pineal gland, but also in the gastrointestinal tract, retina, lacrimal glands, skin, erythrocytes, platelets, lymphocytes, and bone marrow mononuclear cells, derived from noradrenergic stimulation of tryptophan and serotonin by α1 and β1 adrenergic receptors in postsynaptic pinealocytes **[10-12]**.

In this sense, individuals with altered melatonin production may develop insulin resistance, glucose intolerance, insulin secretion disorders, dyslipidemia, energy balance disorders, and obesity **[13]**. Furthermore, the usual metabolism of the daily distribution of sleep/wake and fasting/eating cycles completely disappears **[14-16]**. It should be noted that the daily metabolic cycle is characterized by a phase that temporally associates increased insulin sensitivity and glucose-stimulated insulin secretion with the fed state. Additionally, there is another phase that associates insulin resistance, mainly hepatic, with subsequent gluconeogenesis during sleep or rest. In this context, both phases disappear completely, characterizing a picture of circadian rhythm disturbance, called photodisruption **[17-24]**.

Also, melatonin secretion decreases with aging and the presence of various diseases **[25]**. The sleep pattern changes throughout life and this has a great impact with advancing age and the development of certain diseases such as obesity and diabetes. Melatonin has been recommended for use in cases of sleep disorders such as insomnia and jet lag. However, pleiotropic actions of melatonin such as metabolic functions, and regulation of obesity and diabetes can be extremely useful in numerous diseases **[26]**.

In this context, Mukherjee et al. proposed that melatonin can provide cardioprotection at low pharmacological doses **[27]**. Melatonin's ability to improve cardiovascular function and its hypotensive effect because of its direct and receptordependent antioxidant actions suggest that melatonin may have some beneficial effects in controlling diabetic vascular complications **[28, 29]**. Furthermore, animal studies have shown that melatonin can reduce body weight and fat mass and regulate energy expenditure, glucose/lipid metabolism, and insulin secretion; therefore, it can play an effective role in weight management **[30-32]**.

Studies suggest a possible role for melatonin in metabolic diseases such as obesity, T2DM, and metabolic syndrome **[27-31]**. However, there is no consensus on melatonin as an adjuvant in the treatment of metabolic diseases. Thus, studies are needed to define the possible risks and benefits of melatonin as a therapeutic agent. In the timeline, melatonin has developed exclusive or non-receptor-mediated forms of action. The immediate mode of action is similar to the classic and well-known hormone-effector interaction. The difference is that, in addition to the immediate measurable effects, melatonin initiates overnight effects that will only be observed the next day, after the signal ends. Furthermore, due to its special mechanisms of synthesis and synchronization with the environmental light/dark cycle, melatonin acts as an internal synchronizer of circadian rhythms **[33]**.

Therefore, the present study aimed to carry out a systematic review of the main effects of melatonin in the treatment of obesity and diabetes mellitus, as well as in the prevention of cardiovascular diseases.

Methods

Study Design

The systematic review rules of the PRISMA Platform were followed. Available at: www.prisma-statement.org/. Accessed: 04/14/2023.

Research Strategy and Research Sources

The literary search process was carried out from April to May 2023 and was developed based on Scopus,

PubMed, Science Direct, Scielo, and Google Scholar, using scientific articles until 2023, using the descriptors (MeSH Terms): *Melatonin. Obesity. Diabetes. Cardiovascular diseases*, and using the Boolean "and" between MeSH terms and "or" between historical findings.

Quality of Studies and Risk of Bias

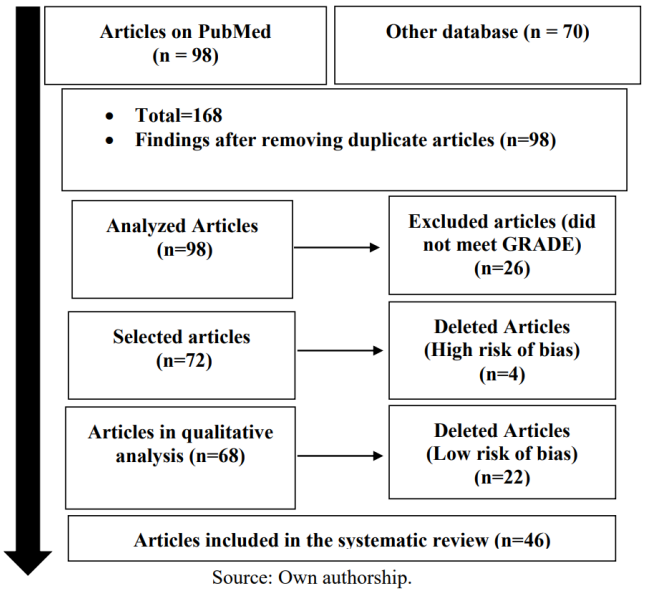
Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. High ranking was for systematic review articles or meta-analysis of RCTs, followed by RCTs. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through Funnel Plot analysis.

Results

Summary of Findings

A total of 168 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 98 articles. A total of 68 articles were evaluated in full and 46 articles were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 4 studies with a high risk of bias and 26 studies that did not meet GRADE. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=90.4%>50%.

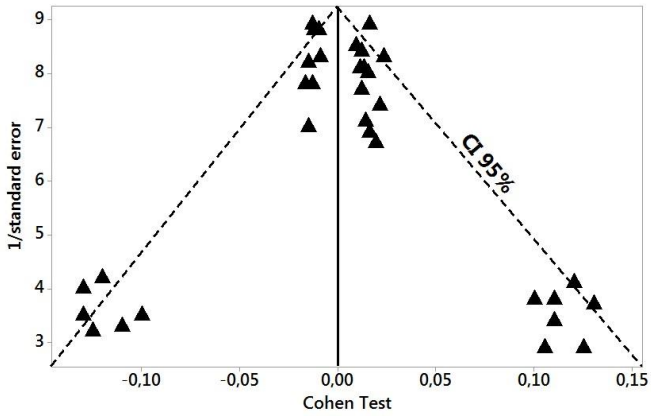
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot. The sample size was indirectly determined by the inverse of the standard error. This graph showed 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 displayed at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (NTotal= 46 studies evaluated in full in the systematic review).



Source: Own authorship.

Highlight Outcomes – Melatonin and Metabolic and Cardiovascular Diseases

Melatonin or N-acetyl-5-methoxytryptamine is a hormone produced by the pineal gland. It is synthesized from serotonin by the initial conversion of tryptophan into serotonin which produces N-acetylserotonin, which molecule will then be converted into melatonin. This hormone works as a circadian rhythm regulator, and is also a potent antioxidant and anti-inflammatory. Melatonin secretion decreases with age and influences seasonal and circadian rhythms, the sleep-wake cycle and reproduction. It has a day/night secretion pattern, sensitive to light, with an increase in the beginning of the night and a decrease at the end of this period. In addition, it participates in several other biological functions, including the control of energy balance with a modulating effect on insulin secretion and action, as well as on lipid metabolism **[3-6]**.

Melatonin is considered an important chronobiotic that influences the circadian distribution of metabolic processes, synchronizing them with the feeding, resting and fasting cycle. In this context, there is a reference to its association with insulin resistance, glucose

intolerance, sleep disorders and circadian metabolic disorganization, characterizing a state of chronological interruption and metabolic diseases with harm to general health. Thus, melatonin replacement may be an important factor in the control of these diseases, as well as in the inflammatory process **[8,9]**.

Melatonin can modulate inflammatory processes by eliminating nitrogen oxide, a molecule involved in tissue injury as a secondary inflammatory mediator. There are reports that melatonin can reduce the synthesis or inhibit other pro-inflammatory mediators, including tumor necrosis factor alpha (TNF-a), interleukin 6 (IL-6) and interleukin 8 (IL-8). In this sense, metabolic and liver diseases become targets of studies with melatonin, aiming to clarify its association with molecular mechanisms, and possible use in clinical practice **[3,9,10]**.

In this context, it is emphasized that obesity is a chronic disease resulting from an imbalance between caloric intake and energy expenditure, triggering excessive accumulation of body fat. It is noted that the global incidence of obesity has increased since 1980, as almost a third of the world's population has this type of dysfunction **[34]**.

Obesity is associated with an increased risk of chronic diseases including type II diabetes mellitus, dyslipidemia, systemic arterial hypertension, cardiovascular disease and some types of cancer. The association of obesity with low-grade chronic inflammation is highlighted, which collaborates with the development of the aforementioned systemic metabolic disorders. Obesity causes several intrinsic and extrinsic signals capable of triggering an inflammatory response in adipose tissue. These mechanisms are commonly considered to be the link between chronic caloric excess and adipose tissue inflammation. Some of these mechanisms include dysregulation of fatty acid homeostasis, local hypoxia, mitochondrial dysfunction, increased size and death of adipose cells, in addition to mechanical stress **[35]**.

It is known that inflammation is related to a state of oxidative stress with a large production of reactive oxygen species, compared to the levels of antioxidants, allowing their action and compromising the natural defense systems. In this context, melatonin has been highlighted for its antioxidant and anti-inflammatory properties. Considering that melatonin modulates several processes involved in obesity, there is reference to the possibility of acquiring benefits from its use in various treatments **[36]**.

There is a growing consensus that the antioxidant and anti-inflammatory properties of melatonin are of great importance in preserving the body's function and homeostasis. Melatonin supplementation during pregnancy may reduce ischemia-induced oxidative damage in the fetal brain, increase offspring survival in inflammatory states, and reduce blood pressure in adult offspring. In adulthood, disturbances in melatonin production negatively impact the progression of cardiovascular risk factors and promote cardiovascular and neurodegenerative diseases. The most studied cardiovascular effects of melatonin are linked to hypertension and myocardial ischemia/reperfusion injury, while the most promising ones are linked to the recovery of control of the components of the metabolic syndrome **[37,38]**.

In this sense, dyslipidemia and hypertension are two complications that can develop in diabetic patients if hyperglycemia, insulin resistance, and weight gain are not controlled. A double-blind, randomized, placebo-controlled study investigated the effects of melatonin supplementation on some risk factors for cardiovascular disease and anthropometric indices in patients with T2DM. A total of 50 T2DM patients were randomly allocated into intervention and control groups who received either two melatonin tablets or a placebo (250 mg) once daily for 8 weeks. Systolic blood pressure (SBP), mean arterial pressure (MAP), pulse pressure (PP), plasma atherogenic index (AIP), weight, body mass index (BMI), waist and waist circumference (WC), shape index (ABSI), abdominal volume index (AVI), body adiposity index (BAI), lipid accumulation product (LAP), conicity index and waist-to-height ratio (WHtR) were evaluated in all patients pre and post-intervention. Melatonin supplementation for 8 weeks significantly decreased mean levels of SBP, MAP, PP, weight, BMI, WC, HC, BAI, AVI, conicity index, and WHtR post-intervention ($p<0.05$). Furthermore, median changes in SBP, MAP, PP, weight, BMI, WC, HC 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 mean ABSI levels in the intervention group. Median ABSI changes were significantly greater in the intervention group compared to the control group ($p < 0.001$). Therefore, melatonin supplement consumption can be effective in controlling blood pressure, including SBP, MAP, and PP, and anthropometric indices (as predictors of obesity) in patients with T2DM **[39]**.

Previous studies have proposed that melatonin can regulate BP through multiple mechanisms. Melatonin can act directly as a free radical scavenger and provide appropriate concentrations of nitrogen oxide (NO), which may indirectly improve endothelial function and reduce the activity of the adrenergic system. Furthermore, it is suggested that melatonin may provide

hypotensive effects by stimulating melatonin receptors in peripheral vessels and in the central nervous system **[40]**.

Still, the AVI is considered an important indicator to assess the accumulation of fat in the abdominal region **[41]**. There is no need to consider body weight in calculating BAI and AVI **[42]**. Furthermore, melatonin supplementation significantly increased ABSI, which can adjust WC for height and weight, while showing a strong correlation with mortality rates.

The study carried out by Amstrup et al. in postmenopausal women indicated that 1 year of melatonin treatment (1 or 3 mg per night) reduced fat mass **[43]**. Kozirog et al. in a survey of patients with metabolic syndrome reported a significant reduction in BMI after taking a melatonin supplement (5 mg/day for 2 months) **[44]**. In the study by Mesri Alamdari et al., participants were supplemented with a daily dose of 6 mg of melatonin along with a low-calorie diet for 40 days. Results revealed that all participants significantly reduced weight, BMI, and waist and hip circumference **[45]**. Likewise, Szewczyk-Golec et al. administered a 30-day calorie-restricted diet combined with melatonin supplementation to obese subjects and reported significant weight loss without affecting BMI **[46]**. Therefore, AVI, ABSI, BAI, and WHR together with BMI can be used as an investigation tool in the field to detect cardiovascular problems.

Conclusion

It was concluded that melatonin can reduce body weight and fat mass and regulate energy expenditure, glucose/lipid metabolism, and insulin secretion; therefore, it can play an effective role in weight management. There is a growing consensus that the antioxidant and anti-inflammatory properties of melatonin are of great importance in preserving the body's function and homeostasis. In adulthood, disturbances in melatonin production negatively impact the progression of cardiovascular risk factors and promote cardiovascular and neurodegenerative diseases. The consumption of melatonin supplements can be effective in controlling blood pressure and anthropometric indices (as predictors of obesity) in patients with T2DM. Furthermore, melatonin has significant effects on ischemia-reperfusion injury, myocardial injury, pulmonary hypertension, hypertension, vascular diseases, valvular heart diseases, and lipid metabolism. As an inexpensive and well-tolerated drug, melatonin could be a new therapeutic option for cardiovascular diseases.

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Not applicable.

Ethical Approval

Not applicable.

Informed consent

Not applicable.

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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@.

References

1. Sociedade Brasileira de Cirurgia Bariátrica e Metabólica (SBCBM). A endoscopia e a obesidade [Internet]. SBCBM. 2019 [cited 2023 March 7]. Available from: https://www.sbcbm.org.br/endoscopia-e-obesidade/
2. Instituto Brasileiro de Geografia e Estatística (IBGE). [cited 2023 April 7]. Available from: http://www.ibge.gov.br.
3. Karamitri A, Jockers R. Melatonin in type 2 diabetes mellitus and obesity. Nat Rev Endocrinol. 2019 Feb;15(2):105-125. doi: 10.1038/s41574-018-0130-1.
4. Boga JA, Caballero B, Potes Y, Perez-Martinez Z, Reiter RJ, Vega-Naredo I, Coto-Montes A. Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. J Pineal Res. 2019 Jan;66(1):e12534. doi: 10.1111/jpi.12534. Epub 2018 Nov 26.
5. Forrestel AC, Miedlich SU, Yurcheshen M, Wittlin SD, Sellix MT. Chronomedicine and type 2 diabetes: shining some light on melatonin. Diabetologia. 2017 May;60(5):808-822. doi: 10.1007/s00125-016-4175-1. Epub 2016 Dec 16.

6. Challet E. Keeping circadian time with hormones. Diabetes Obes Metab. 2015 Sep;17 Suppl 1:76-83. doi: 10.1111/dom.12516.
7. Davies SK, Ang JE, Revell VL, Holmes B, Mann A, Robertson FP, et al. Effect of sleep deprivation on the human metabolome. Proc Natl Acad Sci U S A. 2014 Jul 22;111(29):10761-6. doi: 10.1073/pnas.1402663111. Epub 2014 Jul 7.
8. Zybina NN, Tikhomirova OV. Disturbances in melatonin secretion and the efficacy of replacement therapy in sleep disorders. Zh Nevrol Psikhiatr Im S S Korsakova. 2018;118 (4. Vyp. 2):92-98. doi: 10.17116/jnevro20181184292.
9. Meng X, Li Y, Li S, Zhou Y, Gan RY, Xu DP, Li HB. Dietary Sources and Bioactivities of Melatonin. Nutrients. 2017 Apr 7;9(4). pii: E367. doi: 10.3390/nu9040367.
10. Rybnikova NA, Haim A, Portnov BA. Does artificial light-at-night exposure contribute to the worldwide obesity pandemic? Int J Obes (Lond). 2016;40(5):815-23.
11. Cho Y, Ryu SH, Lee BR, Kim KH, Lee E, Choi J. Effects of artificial light at night on human health: A literature review of observational and experimental studies applied to exposure assessment. Chronobiol Int. 2015;32(9):1294-310.
12. Macchi MM, Bruce JN. Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol. 2004;25(3-4):177-95.
13. Bartness TJ, Goldman BD. Peak duration of serum melatonin and short-day responses in adult Siberian hamsters. Am J Physiol. 1988;255(5 Pt 2):R812-22.
14. Lynch GR, Epstein AL. Melatonin induced changes in gonads; pelage and thermogenic characters in the white-footed mouse, Peromyscus leucopus. Comp Biochem Physiol C. 1976;53(2):67-8.
15. Fernández Vázquez G, Reiter RJ, Agil A. Melatonin increases brown adipose tissue mass and function in Zücker diabetic fatty rats: implications for obesity control. J Pineal Res. 2018:e12472.
16. Diaz B, Blázquez E. Effect of pinealectomy on plasma glucose, insulin and glucagon levels in the rat. Horm Metab Res. 1986;18(4):225-9.
17. Mellado C, Rodríguez V, de Diego JG, Alvarez E, Blázquez E. Effect of pinealectomy and of diabetes on liver insulin and glucagon receptor concentrations in the rat. J Pineal Res. 1989;6(4):295-306.
18. Cipolla-Neto J. O papel da melatonina no controle do metabolismo energético: ações centrais, periféricas e a regulação da função metabólica. Projeto Temático FAPESP. 2016.
19. Korkmaz A, Topal T, Tan DX, Reiter RJ. Role of melatonin in metabolic regulation. Rev Endocr Metab Disord. 2009;10(4):261-70.
20. Picinato MC, Haber EP, Cipolla-Neto J, Curi R, de Oliveira Carvalho CR, Carpinelli AR. Melatonin inhibits insulin secretion and decreases PKA levels without interfering with glucose metabolism in rat pancreatic islets. J Pineal Res. 2002;33(3):156-60.
21. Ha E, Yim SV, Chung JH, Yoon KS, Kang I, Cho YH, Baik HH. Melatonin stimulates glucose transport via insulin receptor substrate-1/phosphatidylinositol 3-kinase pathway in C2C12 murine skeletal muscle cells. J Pineal Res. 2006;41(1):67-72.
22. Prunet-Marcassus B, Desbazeille M, Bros A, Louche K, Delagrange P, Renard P, Casteilla L, Pénicaud L. Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. Endocrinology. 2003;144(12):5347-52.
23. Cipolla-Neto J, Amaral FGD. Melatonin as a Hormone: New Physiological and Clinical Insights. Endocr Rev. 2018 Dec 1;39(6):990-1028. doi: 10.1210/er.201800084.
24. Suofu Y, Li W, Jean-Alphonse FG, Jia J, Khattar NK, Li J, Baranov SV, Leronni D, Mihalik AC, He Y, Cecon E, Wehbi VL, Kim J, Heath BE, Baranova OV, Wang X, Gable MJ, Kretz ES, Di Benedetto G, Lezon TR, Ferrando LM, Larkin TM, Sullivan M, Yablonska S, Wang J, Minnigh MB, Guillaumet G, Suzenet F, Richardson RM, Poloyac SM, Stolz DB, Jockers R,Witt-Enderby PA, Carlisle DL, Vilardaga JP, Friedlander RM. Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. Proc Natl Acad Sci USA. 2017;114(38):E7997–E8006.
25. Vriend J, Reiter RJ. Melatonin feedback on clock genes: a theory involving the proteasome. J Pineal Res. 2015;58(1):1–11.
26. Majidinia M, Sadeghpour A, Mehrzadi S, Reiter RJ, Khatami N, Yousefi B. Melatonin: a pleiotropic molecule that modulates DNA damage response and repair pathways. J Pineal Res. 2017;63(1):e12416.
27. Mukherjee D, Roy SG, Bandyopadhyay A, Chattopadhyay A, Basu A, Mitra E, Ghosh AK, Reiter RJ, Bandyopadhyay D. Melatonin protects against isoproterenol-induced myocardial injury in the rat: antioxidative mechanisms. J Pineal Res. 2010;48(3):251–262. doi: 10.1111/j.1600-

079X.2010.00749.x.

28. Simko F, Paulis L. Melatonin as a potential antihypertensive treatment. J Pineal Res. 2007;42(4):319–322. doi: 10.1111/j.1600-079X.2007.00436.x.
29. Erşahin M, Şehirli Ö, Toklu HZ, Süleymanoglu S, Emekli-Alturfan E, Yarat A, Tatlıdede E, Yeğen BÇ, Şener G. Melatonin improves cardiovascular function and ameliorates renal, cardiac and cerebral damage in rats with renovascular hypertension. J Pineal Res. 2009;47(1):97–106. doi: 10.1111/j.1600079X.2009.00693.x.
30. Cipolla-Neto J, Amaral FG, Afeche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: a review. J Pineal Res. 2014;56(4):371–381. doi: 10.1111/jpi.12137.
31. Nduhirabandi F, et al. Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. J Pineal Res. 2011;50(2):171–182.
32. Puchalski SS, Green JN, Rasmussen DD. Melatonin effect on rat body weight regulation in response to high-fat diet at middle age. Endocrine. 2003;21(2):163– 167. doi: 10.1385/ENDO:21:2:163.
33. Mayo JC, Sainz RM, Gonz´ alez Menendez P, Cepas V, Tan DX, Reiter RJ. Melatonin and sirtuins: a "not-so unexpected" relationship. J Pineal Res. 2017;62(2): e12391.
34. Fittipaldi-Fernandez RJ, Zotarelli-Filho IJ, Diestel CF, Klein MRST, de Santana MF, de Lima JHF, Bastos FSS, Dos Santos NT. Randomized Prospective Clinical Study of Spatz3® Adjustable Intragastric Balloon Treatment with a Control Group: a Large-Scale Brazilian Experiment. Obes Surg. 2021 Feb;31(2):787-796. doi: 10.1007/s11695-020-05014-0.
35. Garcia Ramirez AV, Filho DR, Zotarelli Filho IJ. Meta-analysis and Approach of the Real Impact of Anorexigenic Drugs in the Obesity in Humans: The Last Five Years of the Randomized Studies. Curr Diabetes Rev. 2020;16(7):750-758. doi: 10.2174/1573399815666191113125247.
36. Fittipaldi-Fernandez RJ, Zotarelli-Filho IJ, Diestel CF, Klein MRST, de Santana MF, de Lima JHF, Bastos FSS, Dos Santos NT. Intragastric Balloon: a Retrospective Evaluation of 5874 Patients on Tolerance, Complications, and Efficacy in Different Degrees of Overweight. Obes Surg. 2020 Dec;30(12):48924898. doi: 10.1007/s11695-020-04985-4.
37. Chitimus DM, Popescu MR, Voiculescu SE, Panaitescu AM, Pavel B, Zagrean L, Zagrean AM. Melatonin's Impact on Antioxidative and Anti-Inflammatory Reprogramming in Homeostasis and Disease. Biomolecules. 2020 Aug 20;10(9):1211. doi: 10.3390/biom10091211.
38. Sun H, Gusdon AM, Qu S. Effects of melatonin on cardiovascular diseases: progress in the past year. Curr Opin Lipidol. 2016 Aug;27(4):408-13. doi: 10.1097/MOL.0000000000000314.
39. Bazyar H, Zare Javid A, Bavi Behbahani H, Moradi F, Moradi Poode B, Amiri P. Consumption of melatonin supplement improves cardiovascular disease risk factors and anthropometric indices in type 2 diabetes mellitus patients: a doubleblind, randomized, placebo-controlled trial. Trials. 2021 Mar 25;22(1):231. doi: 10.1186/s13063-021-05174-z.
40. Paulis L, Šimko F. Blood pressure modulation and cardiovascular protection by melatonin: potential mechanisms behind. Physiol Res. 2007;56(6):671-84.
41. Vuga, M., Conceptual review of issues with practical abdominal obesity measures. Section on Statistics in Epidemiology-JSM, 2009:4876-90.
42. López AA, Cespedes ML, Vicente T, Tomas M, Bennasar-Veny M, Tauler P, Aguilo A. Body adiposity index utilization in a Spanish Mediterranean population: comparison with the body mass index. PLoS One. 2012;7(4):e35281. doi: 10.1371/journal.pone.0035281.
43. Amstrup AK, Sikjaer T, Pedersen SB, Heickendorff L, Mosekilde L, Rejnmark L. Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women: a randomized placebo-controlled trial. Clin Endocrinol. 2016;84(3):342–347. doi: 10.1111/cen.12942.
44. Koziróg M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res. 2011;50(3):261–266. doi: 10.1111/j.1600-079X.2010.00835.x.
45. Alamdari NM, et al. A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. Horm Metab Res. 2015;47(07):504–508.

46. Szewczyk-Golec K, Rajewski P, Gackowski M, Mila-Kierzenkowska C, Wesołowski R, Sutkowy P, Pawłowska M, Woźniak A. Melatonin supplementation lowers oxidative stress and regulates adipokines in obese patients on a calorie-restricted diet. Oxidative Med Cell Longev. 2017;2017:1– 10. doi: 10.1155/2017/8494107.