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# Major clinical outcomes of melatonin regulation in obesity: a systematic review

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## Abstract

**Introduction:** In the scenario of non-communicable chronic diseases, obesity has briefly impacted the global population, causing serious public health problems. There are approximately 2.0 billion overweight and obese people in the world. Brazil ranks fifth in the world with approximately 18.0 million people. Research has advanced on the physiological role of melatonin (MEL) as a therapeutic agent for the treatment of obesity. **Objective:** It was to highlight the main clinical outcomes of melatonin regulation in obesity through a systematic review of the literature. **Methods:** The present study followed a concise systematic review model, following the systematic review rules (PRISMA). The literary search process was carried out from September to October 2022 and developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar. 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. **Results and Conclusion:** It was founded 139 studies were submitted to the eligibility analysis, then, 46 of the 54 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with I2 =98.4% >50%. Studies have shown an important role for melatonin in metabolic diseases such as obesity, type 2 diabetes mellitus, and metabolic syndrome. It is possible to define some pathological syndromes related to MEL and discuss general guidelines for clinical therapy. However, there is still no consensus on the possible role of melatonin as an adjuvant in the treatment of metabolic diseases. More studies are needed to define the possible risks and benefits of melatonin as a therapeutic agent. Furthermore, several precautions must be taken into account, such as restricting the administration of chronic melatonin to the night, carefully choosing the time of administration according to the desired effect, and adapting the dosage and formulation individually to build a melatonin blood profile that mimics the physiological and ends early in the morning.

**Keywords:** Obesity. Metabolic syndrome. Type 2 diabetes mellitus. Melatonin. Regulation.

## Introduction

In the scenario of non-communicable chronic diseases, obesity has briefly impacted the global population, causing serious public health problems [1]. In this scenario, there are about 2.0 billion overweight and obese people in the world [1]. Brazil ranks fifth in the world with an estimated 18.0 million people [2].

In this context, research has advanced on the physiological role of melatonin (MEL) and its pharmacological analogues as therapeutic agents for the treatment of various pathologies, mainly obesity, metabolic diseases and diabetes [3-5]. 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 [6,7].

The sleep-wake cycle is critical for the secretion and physiological variations of several hormones, including MEL [8]. Indolaminergic melatonin (N-acetyl-5-methoxytryptamide) 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 $\alpha 1$ and $\beta 1$ adrenoreceptors in postsynaptic pinealocytes [9].

In this sense, individuals who have absence or reduced MEL production may develop insulin resistance,

glucose intolerance, insulin secretion disorders, dyslipidemia, energy balance disorders and obesity. Furthermore, the usual daily distribution of metabolism associated with the sleep-wake cycle and the fasting-food intake cycle completely disappears [10]. Thus, the daily metabolic cycle is characterized by a phase that temporally associates increased insulin sensitivity and an increase in its secretion stimulated by glucose with the large daily bout of eating, and by another phase that associates insulin resistance, mainly hepatic, and subsequent gluconeogenesis. to the period of sleep or rest, it disappears completely, characterizing a picture where there is a disturbance of the circadian rhythm, called chronorupture [11].

Unlike other hormonal axes, MEL secretion is not regulated by feedback and, for this reason, its plasma concentrations do not depend on its production. The secretion of the pineal gland has its control influenced by the circadian cycle in the suprachiasmatic nucleus of the hypothalamus and, consequently, promotes the peak of MEL secretion during the night and during the day it decreases due to exposure to light [12].

Added to this, MEL has endocrine and paracrine actions and binds to three receptors, central and peripheral, in various parts of the body [12]. 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 reduced cyclic GMP monophosphate (cGMP), respectively. MT3, recently discovered nuclear receptor of the retinoic acid family (RZR/ROR), has a structure of the quinone reductase type with a function that is still not fully understood [13].

Furthermore, there is a decrease in MEL secretion with aging and the presence of various diseases [13]. The sleep pattern undergoes changes and this has a great impact with advancing age and the development of certain diseases such as obesity and 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 various diseases [14].

Therefore, the present study aimed to highlight the main clinical outcomes of melatonin regulation in obesity through a systematic review of the literature

## Methods

### Study Design

The systematic review rules of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

### Data sources and research strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Obesity. Metabolic syndrome. Type 2 diabetes mellitus. Melatonin. Regulation". The research was carried out from September to October 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the operator "NOT" were used to target scientific articles of interest.

### Study quality and risk of bias

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 Discussion

### Summary of Findings

A total of 139 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 76 articles. A total of 54 articles were evaluated in full and 46 were included and developed in this systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22 studies with a high risk of bias and 36 studies that did not meet GRADE. Most of the selected studies showed homogeneity in their results, with I2 =98.4% >50%.

Figure 1. Flowchart showing the article selection process.

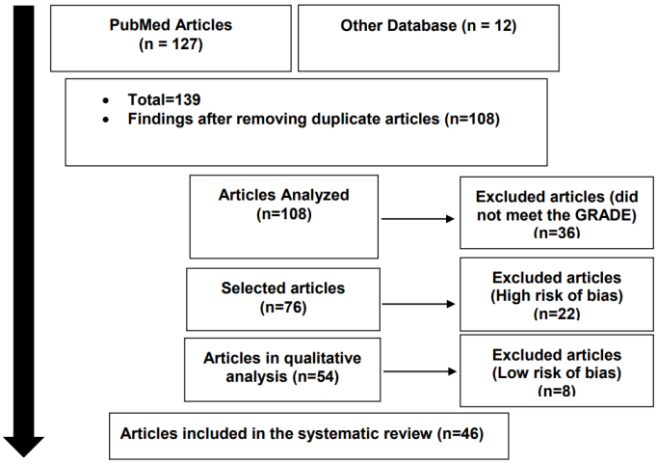
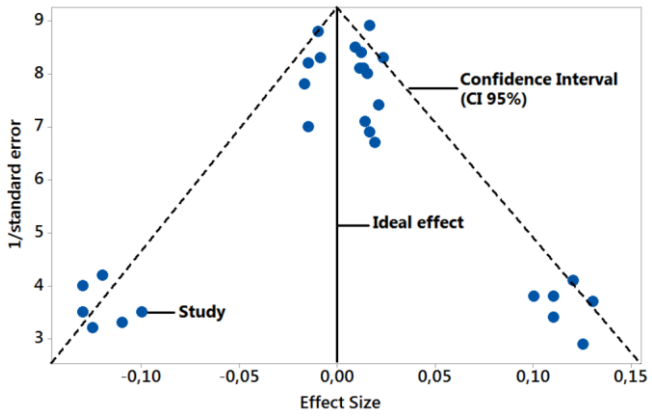



Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot (Effect Size (Magnitude of the difference) Cohen`Test (d)). The sample size was indirectly determined by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting 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).




## Clinical Findings

Based on literary findings, despite the importance of the genetic role in energy metabolism, environmental variables have a strong impact on the global obesity epidemic. Although the greater emphasis is given to poor diet and physical inactivity, other causes have been linked, such as sleep deprivation [13]. In recent years, there has been a significant reduction in hours of sleep and recent epidemiological studies show the relationship between short hours of sleep and increased body mass index. Several studies point to a greater risk of developing obesity in people who sleep less than six hours a day [14-16].

Studies suggest a direct and indirect action of MEL in important stages of the biological cycle of adipocytes such as lipolysis, lipogenesis, adipocyte differentiation, and uptake of free fatty acids and insulin action in these adipose cells through MT1 and MT2 receptors [15,16]. Although the main stimulus for the noradrenergic pineal gland is activated by the absence of light, other peptides can modulate MEL secretion, such as a 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 [17].

In this context, the increase in appetite after sleep deprivation in people who work the night shift is remarkable [18]. The hormonal changes that occur during sleep deprivation may explain the increase in caloric intake and decrease in leptin (anorectic hormone) and increase in ghrelin and peptide YY (orexigenic hormones). In addition, the reduction in sleep time seems to change the preference for high-calorie foods and reduce energy expenditure. Seasonal changes are also related to sleep, MEL levels, and weight gain [19].

In addition to regulating body weight, MEL regulates energy balance. Thus, all energy ingested through food is used or stored in energy stores for future use. There is solid experimental evidence showing that MEL acts by regulating each of the energy balance steps [19]. In this sense, MEL is a hormone that, mainly through central action, regulates food intake, regulating the production and secretion of insulin, glucagon, and cortisol, thus organizing the flow of energy reserves to and from stocks and also increasing 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 [20].

Thus, as a chronobiotic and cytoprotective agent, MEL occupies a special place in the prevention and treatment of metabolic syndrome. As mitochondrial activity is modulated by energy availability in cells, disruption of key metabolism 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, in part due to its role as a metabolic regulator and mitochondrial protector [12].

## Analytical Studies of Melatonin in Obesity and Type 2 Diabetes Mellitus

With the increase in obesity, consequently, there is an increase in complications such as type 2 diabetes mellitus (T2DM) [17]. As we previously reported, MEL plays an important role in insulin signaling and its lack has diabetogenic effects [18-20]. Epidemiological studies also show a link between sleep deprivation, insulin resistance, and T2DM. Nurses' Health Study cohort analysis 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 [17]. The same urinary metabolite is also decreased in diabetic patients with diabetic retinopathy compared to patients without this microvascular complication [17].

Besides, MEL is an important player in the regulation of energy metabolism, including body weight,

insulin sensitivity, and glucose tolerance [21]. In this sense, MEL regulates energy metabolism, acting at all stages of energy balance, including energy consumption, the energy flow to and from stores, and energy expenditure. Furthermore, MEL, through its chronobiotic and seasonal effects, synchronizes energy metabolism requirements with daily and annual rhythms [22, 23].

Thus, the circadian distribution of energy allows the synchronization of typical behaviors associated with the capture of energy that occurs during the activity/wake of the day, with physiological and metabolic modifications that guarantee the use and storage of energy for later use [24]. This fair daily is associated with high central and peripheral insulin sensitivity and high glucose tolerance, increased insulin secretion, high glucose uptake by insulin-sensitive tissues, glycogen synthesis and glycolysis (hepatic and muscle), blockade of hepatic gluconeogenesis, increased adipose tissue lipogenesis and adiponectin production [25].

The complementary rest/sleep phase of the day is characterized by fasting associated with the consequent use of stored energy to maintain life [26]. This phase of the daily cycle of energy metabolism exhibits glucose reduction and pancreatic incretin-induced insulin release, insulin resistance, marked hepatic gluconeogenesis and glycogenolysis, adipose tissue lipolysis, and leptin secretion [27]. The energy imbalance in body weight reduction is probably due to the action of MEL on hypothalamic food input circuits, intensifying anorexigenic signals and decreasing orexigenic signals [28]. In postmenopausal overweight women, there is a negative correlation between levels of the urinary metabolite MEL (6-sulphatoxymelatonin) and BMI [28].

Furthermore, in a randomized placebo-controlled trial, chronic daily administration of MEL in postmenopausal women induced a reduction in fat mass and an increase in lean mass [24]. In other randomized clinical trials, MEL treatment was able to counteract the usual metabolic effects of second-generation antipsychotic drugs, such as olanzapine and clozapine, including agents mitigating weight gain and reducing body fat mass, triglycerides, and total cholesterol levels. [25-29].

The importance of regular daily MEL secretion, determining high insulin sensitivity during the day, is well demonstrated by several clinical and epidemiological studies, showing an association between low MEL production and insulin resistance [30-36]. Thus, despite considerable advances in recent years, obesity and T2DM remain two major challenges for public health systems around the world. Over the past 9 years, genome-wide association studies have established an important role for genetic variation within the MTNR1B locus in regulating fasting plasma glucose levels and T2DM risk [37].

Based on this scenario and as literary support, a review study discussed the effect of MEL and its receptors on glucose homeostasis, obesity, and T2DM [6]. Preclinical and clinical evidence of frequent and rare variants of the MTNR1B locus confirmed its importance in regulating glucose homeostasis and T2DM risk with minor effects on obesity. However, these studies have not resolved the question of whether MEL is beneficial or harmful, an issue that will be discussed in the context of the peculiarities of the melatonergic system. Therefore, MEL receptors may have therapeutic potential, as they belong to the highly druggable G protein-coupled receptor superfamily. It is urgent to clarify the precise role of MEL and its receptors in glucose homeostasis, as MEL is widely used for other indications [6].

Another study identified associations between normal and overweight and/or obese adults between circadian timing (onset of MEL in low light; DLMO) and circadian misalignment (the interval between DLMO and sleep onset) with the risk of metabolic disease. Participants aged 18 to 50 years without depression, diabetes, or shift work, with sleep duration of 6.5 h or more. Analyzes were performed for the entire sample (n = 54) and stratified by normal weight (n=36) and overweight/obesity (n = 18) groups. The mean age was 26.4 years (SD = 7.1 years). Mean sleep duration was 436.2 min (SD = 55.1 min), DLMO was 2250 h (SD=01:31), and the interval between DLMO and sleep onset was 2 h 18 min (SD = 53 min). The mean BMI was 24.3 kg/m2 (SD = 4.5 kg/m2). Circadian time and the interval between DLMO and sleep onset were not associated with glucose, insulin, or HOMA-IR in the main analyses. Among overweight/obese participants, a shorter interval between DLMO and sleep onset was associated with higher insulin (p = 0.04) and HOMAIR (p = 0.04). Therefore, results indicated that among overweight/obese participants, insulin was 5.1 pmol/L higher and HOMA was 1.3 μU/mL higher with each hour closer to sleep onset than DLMO [11].

Therefore, circadian disruption as a result of shift work or jet lag can disrupt this continuity and lead to or worsen obesity and metabolic diseases. MEL affects pancreatic β-cell insulin secretory activity, hepatic glucose metabolism, and insulin sensitivity. Individuals with T2DM have lower serum levels of MEL at night and a greater risk of sleep disorders compared to healthy individuals. Furthermore, reduced levels of MEL and mutations and/or genetic polymorphisms of MEL receptors are associated with an increased risk of

developing T2DM [7].

### Melatonin and Regulation of Obesity and Diabetes

A review study showed that at the beginning of 2018, there were 3000 to 4000 clinical studies (1000 in the last 5 years) using MEL, among which almost 200 were randomized clinical trials. Furthermore, from 1996 to July 2017, there were 195 narrative and systematic reviews on the effects of the clinical use of MEL [38].

Thus, the time domain is a critical factor to be considered in chronic MEL treatments [39], as the molecule has the unique characteristic of being a hormone that regulates the body's physiology and behavior [40]. The physiological production of MEL is precisely every day and the initiation of its synthesis helps to adjust the circadian time for the central clock, concomitantly triggering the night for the CNS and peripheral targets [41].

In addition to daily and seasonal variation in the time domain of the MEL signal, every organism has a specific ontogenetic history of the magnitude of the daily peak of MEL production [42]. Furthermore, it should be considered that the MEL profile is unique for each person. For each individual, the timing, amplitude, and even details of the MEL profile must be highly reproducible from day to day and week to week, both in experimental or clinical studies and treatments, as the effects of the MEL will depend on the time and route of administration, on the concentration and duration of the signal, on the regularity of the daily repetition flow and the characteristics of the target organ [43].

In this sense, adipocytes secrete pro-inflammatory cytokines, as well as leptin, and trigger a vicious circle that leads to further weight gain mainly as fat [44]. The imbalance between inflammatory and anti-inflammatory signals is crucial for aging. Healthy aging can benefit from MEL, a compound known to possess direct and indirect antioxidant properties, to have a significant protective effect on mitochondrial function, to increase circadian rhythm amplitude, to modulate the immune system, and to exhibit neuroprotective actions [45]. MEL levels decrease in the course of senescence and are more strongly reduced in diseases related to insulin resistance.

Finally, a review article analyzed the multiple protective actions of MEL that are relevant to the attenuation of inflammatory responses and inflammation progression and how MEL is effective in reducing hyper adipose metabolic syndrome. As attention has been focused on the development of potent MEL analogs as noted above and with prolonged effects and in clinical trials, these analogs have been administered at considerably higher doses than those generally employed for MEL, clinical trials on MEL in the range 50-100 mg/day are needed to further assess its therapeutic value in the metabolic syndrome [46].

## Conclusion

Studies have shown an important role for melatonin in metabolic diseases such as obesity, T2DM, and metabolic syndrome. It is possible to define some pathological syndromes related to MEL and discuss general guidelines for clinical therapy. However, there is still no consensus on the possible role of melatonin as an adjuvant in the treatment of metabolic diseases. More studies are needed to define the possible risks and benefits of melatonin as a therapeutic agent. Furthermore, several precautions must be taken into account, such as restricting the administration of chronic melatonin to the night, carefully choosing the time of administration according to the desired effect, and adapting the dosage and formulation individually to build a melatonin blood profile that mimics the physiological and ends early in the morning.

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## Ethics approval

Not applicable.

## Informed consent

Not applicable.

## 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. WHO- World Health Organization. Available at: https://www.sbcbm.org.br/endoscopye-obesidade/

Accessed in October 2022.
2. IBGE- Brazilian Institute of Geography and Statistics. Available at: http://www.ibge.gov.br. Accessed October 2022.
3. Guan Q, Wang Z, Cao J, Dong Y, Chen Y. Mechanisms of Melatonin in Obesity: A Review. Int J Mol Sci. 2021 Dec 25;23(1):218. doi: 10.3390/ijms23010218.
4. Pivonello C, Negri M, Patalano R, Amatrudo F, Montò T, Liccardi A, Graziadio C, Muscogiuri G, Pivonello R, Colao A. The role of melatonin in the molecular mechanisms underlying metaflammation and infections in obesity: A narrative review. Obes Rev. 2022 Mar;23(3):e13390. doi: 10.1111/obr.13390.
5. Xu L, Li D, Li H, Zhang O, Huang Y, Shao H, Wang Y, Cai S, Zhu Y, Jin S, Ding C. Suppression of obesity by melatonin through increasing energy expenditure and accelerating lipolysis in mice fed a high-fat diet. Nutr Diabetes. 2022 Oct 7;12(1):42. doi: 10.1038/s41387-022-00222-2.
6. 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.
7. Boga JA, Caballero B, Potes Y, Perez-Martinez Z, Reiter RJ, Vega-Naredo I, CotoMontes 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.
8. 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 162. doi: 10.1016/j.ijom.2022.05.014.
9. Challet E. Keeping circadian time with hormones. Diabetes Obes Metab. 2015 Sep;17 Suppl 1:76-83. doi: 10.1111/dom.12516.
10. Davies SK, Ang JE, Revell VL, Holmes B, Mann A, Robertson FP, Cui N, Middleton B, Ackermann K, Kayser M, Thumser AE, Raynaud FI, Skene DJ. 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.
11. Al-Sarraf IAK, Kasabri V, Akour A, Naffa R. Melatonin and cryptochrome 2 in metabolic syndrome patients with or without diabetes: a cross-sectional study. Horm Mol Biol Clin Investig. 2018 May 29;35(2). pii: /j/hmbci.2018.35.issue-2/hmbci-2018-0016/hmbci2018-0016.xml. doi: 10.1515/hmbci-2018-0016.
12. Baron KG, Reid KJ, Wolfe LF, Attarian H, Zee PC. Phase Relationship between DLMO and Sleep Onset and the Risk of Metabolic Disease among Normal Weight and Overweight/Obese Adults. J Biol Rhythms. 2018 Feb;33(1):76-83. doi: 10.1177/0748730417745914. Epub 2017 Dec 20.
13. Cardinali DP, Vigo DE. Melatonin, mitochondria, and the metabolic syndrome. Cell Mol Life Sci. 2017 Nov;74(21):3941-3954. doi: 10.1007/s00018-017-2611-0. Epub 2017 Aug 17.
14. Rao PV. Type 2 diabetes in children: clinical aspects and risk factors. Indian J Endocrinol Metab 2015; 19(Suppl1): S47-S50.
15. Milcu I, Nanu L, Marcean R et al. The action of pineal extract and epiphysectomy on hepatic and muscular glycogen after prolonged infusion of glucose. Stud Cercet Endocrinol 1963; 14: 651-655.
16. Zanquetta MM, Seraphim PM, Sumida DH et al. Calorie restrictionreduces pinealectomyinduced insulin resitance by improving GLUT4 gene expression and its translocation to the plasma membrane. J Pineal Res 2003; 35: 141-148.
17. Ghosh G, De K, Maity S et al. Melatonin protects against oxidative damage and restores expression of GLUT4 gene in the hyperthyroid rat heart. J Pineal Res 2007; 42: 343-350.
18. 18. McMullan CJ, Schernhammer ES, Rimm EB et al. Melatonin secretion and the incidence of tye 2 diabetes. JAMA 2013; 109(13): 1388-1396.
19. Chen W, Cao H, Lu QY et al. Urinary 6-sulfatoxymelatonin level in diabetic retinophaty patients with type 2 diabetes. Int J Clin Exp Pathol 2014; 7(7): 4317-4322.
20. Chen W, Cao H, Lu QY et al. Urinary 6-sulfatoxymelatonin level in diabetic retinophaty patients with type 2 diabetes. Int J Clin Exp Pathol 2014; 7(7): 4317-4322.
21. National Sleep Foundation. 2002 "Sleep in America" Poll. Washington DC: National Sleep Foundation, 2002.
22. Vorona R, Winn M, Babineau T et al. Overweight and obese patients in a primary care population report less sleep than patients wiht a normal body mass index. Arch Inter Med 2005; 165: 25-30.
23. Dempsey JA, Veasay SC, Morgan BJ et al. Pathophysiologicy of sleep apnea. Physiol Rev 2010; 90(1): 47-112.
24. Lucassen EA, Rother KI, Cizza G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. Ann NYAcad Sci 2012; 1264: 110-134.

25. 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 (Oxf). 2016;84(3):342–347.
26. Romo-Nava F, Alvarez-Icaza Gonz´ alez D, Fres´ anOrellana A, Saracco Alvarez R, Becerra-Palars C, Moreno J, Ontiveros Uribe MP, Berlanga C, Heinze G, Buijs RM. Melatonin attenuates antipsychotic metabolic effects: an eight-week randomized, doubleblind, parallel-group, placebo-controlled clinical trial. Bipolar Disord. 2014;16(4):410–421.
27. Agahi M, Akasheh N, Ahmadvand A, Akbari H, Izadpanah F. Effect of melatonin in reducing second-generation antipsychotic metabolic effects: a double blind controlled clinical trial. Diabetes Metab Syndr. 2018;12(1):9–15.
28. Kamath A, Rather ZA. Melatonin for atypical antipsychotic-induced metabolic adverse effects: a meta-analysis of randomized controlled trials. BioMed Res Int. 2018;2018:4907264.
29. Mohammadi-Sartang M, Ghorbani M, Mazloom Z. Effects of melatonin supplementation on blood lipid concentrations: a systematic review and metaanalysis of randomized controlled trials [published online ahead of print 16 November 2017]. Clin Nutr. doi: 10.1016/j.clnu.2017.11.003.
30. Mostafavi SA, Solhi M, Mohammadi MR, Akhondzadeh S. Melatonin for reducing weight gain following administration of atypical antipsychotic olanzapine for adolescents with bipolar disorder: a randomized, double-blind, placebocontrolled trial. J Child Adolesc Psychopharmacol. 2017;27(5):440–444.
31. Zheng C, Dalla Man C, Cobelli C, Groop L, Zhao H, Bale AE, Shaw M, Duran E, Pierpont B, Caprio S, Santoro N. A common variant in the MTNR1b gene is associated with increased risk of impaired fasting glucose (IFG) in youth with obesity. Obesity (Silver Spring). 2015;23:1022–1029.
32. Zhan Y, Li C, Gao Q, Chen J, Yu S, Liu SG. Association between the rs4753426 polymorphism in MTNR1B with fasting plasma glucose level and pancreatic b-cell function in gestational diabetes mellitus. Genet Mol Res. 2015;14(3): 8778–8785.
33. Lane JM, Chang AM, Bjonnes AC, Aeschbach D, Anderson C, Cade BE, Cain SW, Czeisler CA, Gharib SA, Gooley JJ, Gottlieb DJ, Grant SF, Klerman EB, Lauderdale DS, Lockley SW, Munch M, Patel S, Punjabi NM, Rajaratnam SM, Rueger M, St Hilaire MA, Santhi N, Scheuermaier K, Van Reen E, Zee PC, Shea SA, Duffy JF, Buxton OM, Redline S, Scheer FA, Saxena R. Impact of common diabetes risk variant in MTNR1B on sleep, circadian, and melatonina physiology. Diabetes. 2016;65(6):1741–1751.
34. Bonnefond A, Froguel P. The case for too little melatonin signalling in increased diabetes risk. Diabetologia. 2017;60(5):823–825. 388.
35. Bonnefond A, Karamitri A, Jockers R, Froguel P. The difficult journey from genomewide association studies to pathophysiology: the melatonin receptor 1B (MT2) paradigm. Cell Metab. 2016;24(3): 345–347.
36. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017;60(5):826–829.
37. Tarnowski M, Malinowski D, Safranow K, Dziedziejko V, Pawlik A. MTNR1A and MTNR1B gene polymorphisms in women with gestational diabetes. Gynecol Endocrinol. 2017;33(5): 395–398.
38. Touitou Y, Reinberg A, Touitou D. Association between light at night, melatonin secretion, sleep deprivation, and the internal clock: Health impacts and mechanisms of circadian disruption. Life Sci. 2017 Mar 15;173:94-106. doi: 10.1016/j.lfs.2017.02.008.
39. Posadzki PP, Bajpai R, Kyaw BM, Roberts NJ, Brzezinski A, Christopoulos GI, Divakar U, Bajpai S, Soljak M, Dunleavy G, Jarbrink K, Nang EEK, Soh CK, Car J. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Med. 2018;16(1):18.
40. Tuomi T, Nagorny CLF, Singh P, Bennet H, Yu Q, Alenkvist I, Isomaa B, Östman B, Söderström J, Pesonen AK, Martikainen S, Räikkönen K, Forsén T, Hakaste L, Almgren P, Storm P, Asplund O, Shcherbina L, Fex M, Fadista J, Tengholm A, Wierup N, Groop L, Mulder H. Increased Melatonin Signaling Is a Risk Factor for Type 2 Diabetes. Cell Metab. 2016 Jun 14;23(6):1067-1077. doi: 10.1016/j.cmet.2016.04.009.
41. J. Cipolla-Neto, F. G. Amaral, S. C. Afeche2, D. X. Tan, R. J. Reiter. Melatonin, energy metabolism, and obesity: a review. J. Pineal Res. 2014, 56:371–381.
42. Fernanda G. Amaral, Ariane O. Turati1, Mark Barone, Julieta H. Scialfa, Daniella do Carmo Buonfiglio, Rafael Peres, Rodrigo A. Peliciari-Garcia, Solange C. Afeche , Larissa Lima , Cristoforo Scavone, Silvana Bordin, Russel J. Reiter, Luiz Menna-Barreto, José Cipolla-Neto.

Melatonin synthesis impairment as a new deleterious outcome of diabetesderived hyperglycemia. J. Pineal Res. 2014, 57:67–79.

43. Moshe Laudon, Anat Frydman-Marom. Therapeutic Effects of Melatonin Receptor Agonists on Sleep and Comorbid Disorders. Int. J. Mol. Sci., 2014, 15: 15924-15950.
44. Ewa Walecka-Kapica, Jan Chojnacki, Agnieszka Stępień, Patrycja Wachowska-Kelly, Grażyna Klupińska and Cezary Chojnacki. Melatonin and Female Hormone Secretion in Postmenopausal Overweight Women. Int. J. Mol. Sci., 2015,16:1030-1042.
45. Thomas Roth, Tali Nir, Nava Zisapel. Prolonged release melatonin for improving sleep in totally blind subjects: a pilot placebo-controlled multicenter trial. Nature and Science of Sleep,2015, 7: 13–23.
46. Nishi T, Saeki K, Obayashi K, Miyata K, Tone N, Tsujinaka H, Yamashita M, Masuda N, Mizusawa Y, Okamoto M, Hasegawa T, Maruoka S, Ueda T, Kojima M, Matsuura T, Kurumatani N, Ogata N. The effect of blue-blocking intraocular lenses on circadian biological rhythm: protocol for a randomised controlled trial (CLOCK-IOL colour study). BMJ Open. 2015 May 12;5(5):e007930. doi: 10.1136/bmjopen-2015-007930.