META-ANALYSIS AND APPROACH OF THE REAL IMPACT OF MELATONIN IN THE OBESITY IN HUMANS: THE LAST TEN YEARS OF THE RANDOMIZED STUDIES

Dr. Idiberto Jose Zotarelli Filho, MSc, Ph.D[1]

[1]Affiliation not available

May 28, 2020

Abstract

Significance: Obesity is a multifactorial disease with many risks to public health, with 39.6% of American adults and 18.5% of young people obese. Brazil ranks fifth in the world rankings, with about 18 million people. In this scenario, melatonin has evidenced an important function in the regulation of energy metabolism. **Information gap:** What is the real influence of melatonin supplementation on obesity and T2DM control? **Objective:** A systematic review of the physiological and endocrine aspects of melatonin was performed, as well as to analyze the real impact of its use for the treatment of obesity and type 2 diabetes in humans. **Methods:** 51 studies were selected to make up the textual part of the manuscript and 44 to make the Meta-analysis. The PRISMA rules followed. **Results and Conclusion:** Many studies have shown the importance of melatonin in various diseases, especially obesity, T2DM and metabolic syndrome. Human studies have shown that the use of melatonin is simple, safe, and has no side effects. Nevertheless, intervention studies using this hormone in obese or diabetic patients do not yet have a consensus on supplementation.

Keywords: Melatonin. Obesity. Metabolism. Type 2 diabetes. Clinical study.

Ana Valéria Garcia Ramirez[1,2], Durval Ribas Filho[2] and Idiberto José Zotarelli Filho[2]

[1] Clinic Ana Valeria Ramirez (CAVR)- Clinical of Nutrition and Health Science, Street Antônio José Martins Filho, 300, 10º floor, room 103, São José do Rio Preto SP, 15092-230, Brazil.

[2] Associação Brasileira de Nutrologia (ABRAN)/Brazilian Association of Nutrology, Catanduva/SP, Rua Belo Horizonte, 909 - Centro, Catanduva SP Brazil 15801-150.

Corresponding Author: Dr. Idiberto José Zotarelli Filho, MsC, Ph.D, São José do Rio Preto SP, Brazil; email: m.zotarelli@gmail.com.

SIGNIFICANCE: 39.6% of American adults and 18.5% of young people are obese. Brazil ranks fifth in the world ranking, with about 18 million people. In this scenario, melatonin has evidenced an important function in the regulation of energy metabolism.

INFORMATION GAP: What is the real influence of melatonin supplementation on obesity control?

OBJECTIVE: A systematic review followed by a meta-analysis of randomized clinical trials over the past ten years to explore the efficacy and safety of melatonin for weight reduction and improves of metabolic disorder.

METHODS: The PRISMA rules and COCHRANE INSTRUMENT were followed. The descriptors "*melatonin, obesity, metabolism, weight loss,* and *clinical trial*" were used.

RESULTS: The results (n = 51) were significant that the imbalance of melatonin can lead to metabolic disorders and circadian rhythmic disorders, p <0.05 (R2 = 94.5%). Also, the studies showed improvement in metabolic disorder, glucose homeostasis, weight loss (> 3.0 kg/month), reduced inflammatory process, and improved sleep after supplementation with or without associated drug melatonin. However, it is not yet known the best concentration to be used in humans, especially in the long-term.

General clinical data of the literary findings analyzed

N total (clinical studies)	Melatonin Dose (mg)_Mean (±SD)	Age_mean (±SD)	BMI	Metabolic Disorder	T2DM	Time of use_mean days (±SD)
51	5,0 (±5,0) (1,0 to 10,0 mg)	45 (±6)	≥30 kg/m^2	Yes=94%	Yes=95%	30 (±4)

Figure 1: This is a caption

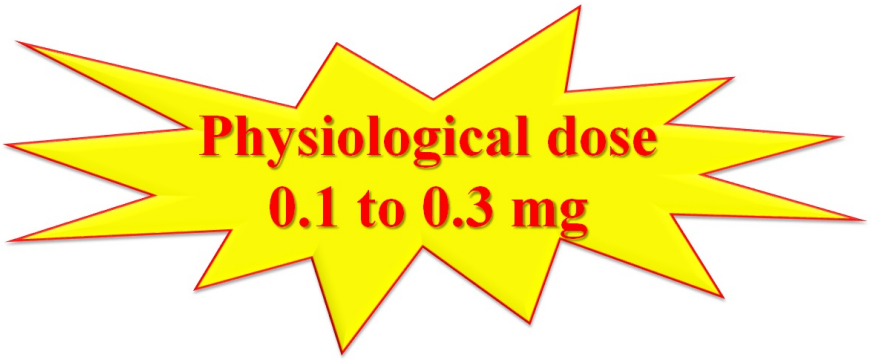


Figure 2: This is a caption

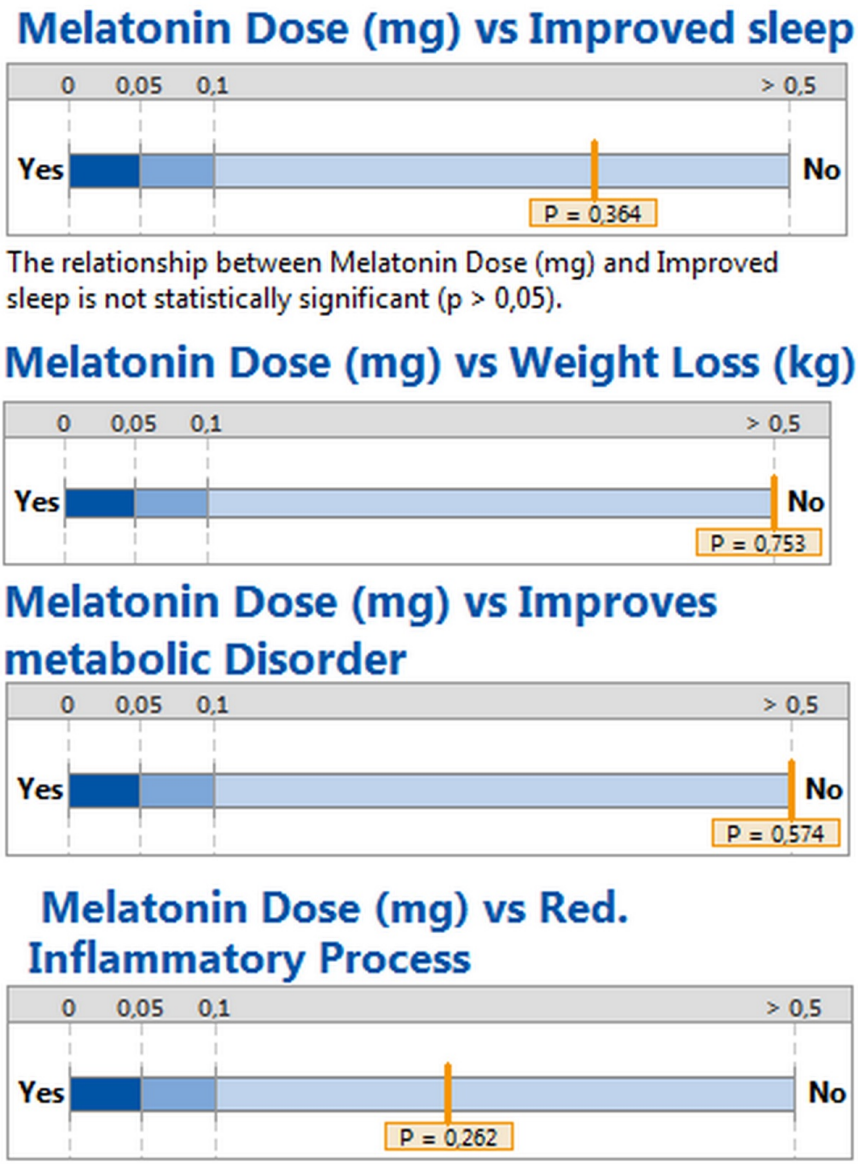


Figure 3: This is a caption

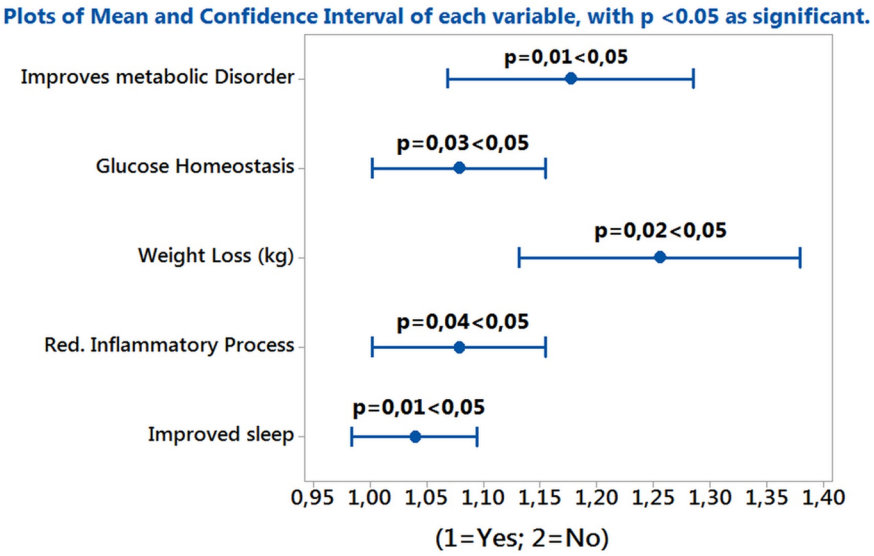
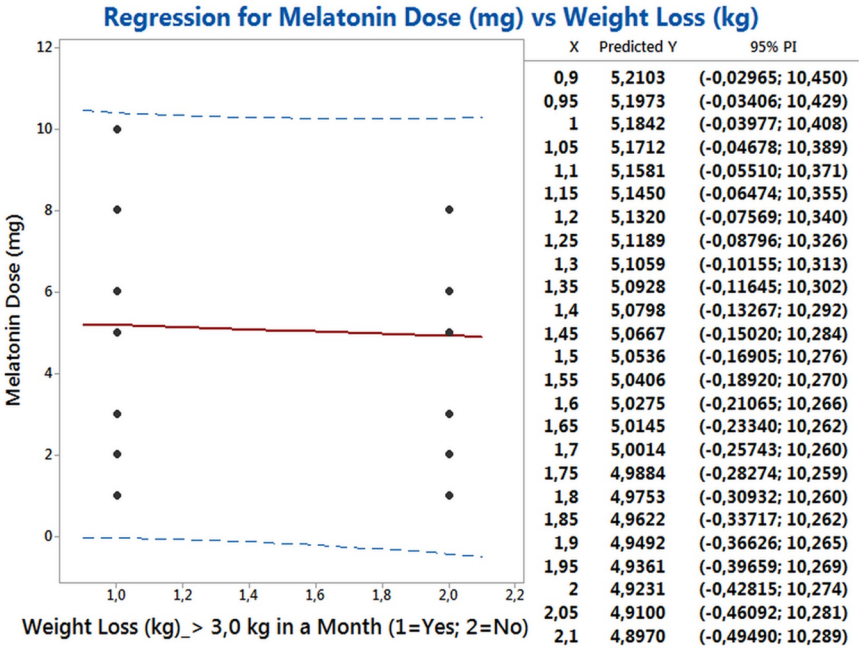


Figure 4: This is a caption



X	Predicted Y	95% PI
0,9	5,2103	(-0,02965; 10,450)
0,95	5,1973	(-0,03406; 10,429)
1	5,1842	(-0,03977; 10,408)
1,05	5,1712	(-0,04678; 10,389)
1,1	5,1581	(-0,05510; 10,371)
1,15	5,1450	(-0,06474; 10,355)
1,2	5,1320	(-0,07569; 10,340)
1,25	5,1189	(-0,08796; 10,326)
1,3	5,1059	(-0,10155; 10,313)
1,35	5,0928	(-0,11645; 10,302)
1,4	5,0798	(-0,13267; 10,292)
1,45	5,0667	(-0,15020; 10,284)
1,5	5,0536	(-0,16905; 10,276)
1,55	5,0406	(-0,18920; 10,270)
1,6	5,0275	(-0,21065; 10,266)
1,65	5,0145	(-0,23340; 10,262)
1,7	5,0014	(-0,25743; 10,260)
1,75	4,9884	(-0,28274; 10,259)
1,8	4,9753	(-0,30932; 10,260)
1,85	4,9622	(-0,33717; 10,262)
1,9	4,9492	(-0,36626; 10,265)
1,95	4,9361	(-0,39659; 10,269)
2	4,9231	(-0,42815; 10,274)
2,05	4,9100	(-0,46092; 10,281)
2,1	4,8970	(-0,49490; 10,289)

Figure 5: This is a caption

CONCLUSION: Melatonin is important for energy regulation and weight loss, but further studies of its supplementation in the control of obesity are needed.

REFERENCES

1. WHO- World Health Organization. Available at: https://www.sbcbm.org.br/endoscopia-e-obesidade/ Accessed: August 2019.

2. IBGE- Instituto Brasileiro de Geografia e Estatística. Disponível em: < http://www.ibge.gov.br>. Acessado em julho de 2019.

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. 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.

5. 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.

6. 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.

7. Challet E. Keeping circadian time with hormones. Diabetes Obes Metab. 2015 Sep;17 Suppl 1:76-83. doi: 10.1111/dom.12516.

8. 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.

9. 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/hmbci-2018-0016.xml. doi: 10.1515/hmbci-2018-0016.

10. 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.

11. 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.

12. Rao PV. Type 2 diabetes in children: clinical aspects and risk factors. Indian J Endocrinol Metab 2015; 19(Suppl1): S47-S50.

13. 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.

14. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.

15. Zanquetta MM, Seraphim PM, Sumida DH et al. Calorie restrictionreduces pinealectomy-induced insulin resitance by improving GLUT4 gene expression and its translocation to the plasma membrane. J Pineal Res 2003; 35: 141-148.

16. 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.

17. McMullan CJ, Schernhammer ES, Rimm EB et al. Melatonin secretion and the incidence of tye 2 diabetes. JAMA 2013; 109(13): 1388-1396.

18. 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.

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. National Sleep Foundation. 2002 "Sleep in America" Poll. Washington DC: National Sleep Foundation, 2002.

21. 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.

22. Dempsey JA, Veasay SC, Morgan BJ et al. Pathophysiologicy of sleep apnea. Physiol Rev 2010; 90(1): 47-112.

23. Lucassen EA, Rother KI, Cizza G. Interacting epidemics? Sleep curtailment, insulin resistance, and obesity. Ann NYAcad Sci 2012; 1264: 110-134.

24. 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.

25. 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, double-blind, parallel-group, placebo-controlled clinical trial. Bipolar Disord. 2014;16(4):410–421.

26. 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.

27. 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.

28. 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.

29. 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.

30. 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.

31. 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.

32. 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.

33. Bonnefond A, Froguel P. The case for too little melatonin signalling in increased diabetes risk. Diabetologia. 2017;60(5):823–825. 388.

34. Bonnefond A, Karamitri A, Jockers R, Froguel P. The difficult journey from genome-wide association studies to pathophysiology: the melatonin receptor 1B (MT2) paradigm. Cell Metab. 2016;24(3): 345–347.

35. Mulder H. Melatonin signalling and type 2 diabetes risk: too little, too much or just right? Diabetologia. 2017;60(5):826–829.

36. 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.

37. 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. Epub 2017 Feb 16.

38. 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.

39. 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. Epub 2016 May 12.

40. 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. 56:371–381, 2014.

41. 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. 57:67–79, 2014.

42. Moshe Laudon, Anat Frydman-Marom. Therapeutic Effects of Melatonin Receptor Agonists on Sleep and Comorbid Disorders. Int. J. Mol. Sci., 15: 15924-15950, 2014.

43. 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., 16:1030-1042, 2015.

44. 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,7: 13–23, 2015.

45. 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.

46. Cardinali DP, Hardeland R. Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies. Neuroendocrinology. 2017;104(4):382-397. doi: 10.1159/000446543. Epub 2016 May 11.