

# Melatonin, menopause, and thyroid function in gynecologic endocrinology: what is the role?

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Melatonin (MTN), a neurohormone primarily synthesized and secreted mainly by the pine cone-shaped gland of the cerebrum, named as the conarium or epiphysis cerebri, from amino acid tryptophan, was first isolated from the bovine pineal gland by Lerner et al<sup>1</sup>. However, the 17th-century philosopher René Descartes hypothesized that the pineal gland of the brain, which remains poorly understood to date, represents the location of the *homo sapiens* soul; paleontologists described it as an ancestral “third eye”; and modern psychology declares perception beyond physical visual function<sup>2,3</sup>. This chemical messenger, *per se*, ensures high precision in the reconnoitering of the night period, is an endocrine marker for darkness, and participates in the regulation of circadian rhythm and the sleep-wake cycle. Of note, MTN can be produced by other organs, such as the brain, lungs, gastrointestinal tract, liver, thyroid, and reproductive and immune systems, and is present in mucus, saliva, breast milk, urine, sperm, amniotic fluid, Graafian follicle, etc.<sup>1,4-9</sup>. As such, various studies have shown that MTN affects many functions in the body and acts on different tissues, and some of its properties include significant antioxidant, anti-inflammatory, antiproliferative, and immunomodulatory capacity. MTN, *per se*, can directly neutralize toxic free radicals more effectively, suppresses chronic oxidative stress, has a significant impact on reproductive cells, enhances the quality of sperm and oocytes, has oncostatic and antitumoral cytoprotective effects<sup>10,11</sup>, alleviates some of the undesirable toxic effects of radiotherapy and chemotherapy by increasing the tolerance of healthy tissues, compared to other antioxidants, by stimulating responses to DNA damage. To this

end, MTN's significant role in some chronic diseases, such as diabetes, blood glucose level regulation, and hypertension, has also been reported. MTN has been studied as a therapeutic option for many autoimmune diseases of multiple sclerosis, rheumatoid arthritis, and diabetes mellitus, based on its immunoregulatory properties. MTN achieves its effect through its receptors type 1 and type 2 (MT1 [Mel<sub>1a</sub>] and MT2 [Mel<sub>1b</sub>]) membrane-bound receptors. Moreover, the presence of the MT1 receptor in the thyroid gland has been proven, which indicates the possibility of MTN's influence on thyroid activity and hormone production. A third membrane-bound MTN-binding site, the MT3 receptor, was theorized as a biological target of MTN and was found to, in fact, act as the cytosolic enzyme, quinone reductase II (NQO2)<sup>12</sup>. Some authors have reported in their genetic study that the single-nucleotide polymorphism of MTN receptor type 1A, MTNR1A, coding the MT1 protein, was associated with a sensitivity to Graves' disease and thyroid autoantibody formation, which supports the impression, that MTN can influence the development of autoimmune thyroid disease in thyroidology<sup>13,14</sup>. The thyroid gland is characterized by a high level of oxidative stress, and the use of pro-oxidants can lead to miscellaneous damage and diseases of this delicate papillon gland. Excessive iodine load, as an exogenous pro-oxidant, can induce apoptosis in the thyroid gland follicular cells. Furthermore, iodine compounds used in iodine prophylaxis also have potentially harmful effects. The thyroid gland is less sensitive to the pro-oxidative effects of potassium iodate, KIO<sub>3</sub>, and reacts more strongly to the antioxidant effect of MTN than other tissues, which plays a significant role in

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this phenomenon. Hence, MTN should be considered to avoid the potential damaging effects of iodine compounds applied in iodine prophylaxis<sup>15-19</sup>. Radiotherapy for head and neck tumors can often damage the thyroid follicular structure even though it is not affected by the tumor. However, administration of MTN before radiotherapy might attenuate the degree of tissue damage. Some authors pointed out the radioprotective effects of MTN in the acute phase of thyroid tissue damage. Besides the aforementioned characteristics, MTN has a crucial role in regulating human reproduction processes, such as oocyte quality, folliculogenesis, oocyte maturation, embryo implantation, fetal development, and the outcomes of pregnancy. Therefore, the idea of MTN utilization in the therapeutic approaches of reproductive and gestational disorders seems favorable to some authorities<sup>20,21</sup>. The low MTN levels in elderly people are correlated with reproductive aging and high gonadotropin secretion, while menopause is characterized by the inability of the ovaries to produce viable follicles and hormonal changes, which leads to menstrual cycle failures. Ovarian aging is characterized by reduced follicular reserve and augmented gonadotropin secretion<sup>22</sup>. In menopause, various alterations emerge in a woman's body, which results in the changes in her mental and physical health statuses. Anecdotally, women experience immuno-metabolic fluctuations, such as hormonal perturbations, sleep problems, and vasomotor symptoms, during menopause. Since MTN is involved in all these processes, it has the potential as a medication with multiple health benefits for the management of a menopausal woman<sup>23,24</sup>. In addition, some authors stated that MTN usage can improve physical symptoms such as sleep quality, mood state, estradiol levels,

and body mass index in a menopausal woman, but not in the general menopausal ones<sup>22</sup>. In summary, MTN appears to play a key role in the regulation of the endocrine system, involving the regulation of gonadotrophin-releasing hormone (GnRH), promotion of progesterone synthesis, stimulation of oxytocin secretion, regulation of cortisol production, and promotion of androgen generation<sup>12</sup>. Nevertheless, it is critical to distinguish between the physiological effects and the pharmacological consequences of MTN administration due to specific differences in the response of any tissue to the agent and to determine whether the stage of development, sex differences, and genetic variability can affect how reproductive tissue responds to MTN by gynecologic endocrinologists and thyroidologists. As a matter of fact, this issue merits further investigation.

## AUTHORS' CONTRIBUTIONS

**JMSJ:** Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Validation, Visualization, Writing – review & editing. **Dzemail D:** Investigation, Project administration, Validation, Visualization, Writing – original draft. **IS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – review & editing. **SD:** Investigation, Validation, Visualization. **DS:** Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Supervision, Writing – review & editing. **Dzenana D:** Investigation, Project administration, Validation, Visualization.

## REFERENCES

- Maliki OF, Alagbon AI, Ibitoye CM, Olayaki LA. Melatonin and vitamin C modulate cassava diet-induced alteration in reproductive and thyroid functions. *Niger J Exp Clin Biosci*. 2021;9:133-43. [https://doi.org/10.4103/njecp.njecp\\_9\\_21](https://doi.org/10.4103/njecp.njecp_9_21)
- Lane R. Of sight, and insight. *Lancet*. 2023;401(10371):97. [https://doi.org/10.1016/S0140-6736\(22\)02589-2](https://doi.org/10.1016/S0140-6736(22)02589-2)
- Soares Junior JM, Kesicioglu T, Sengul D, Sengul I. Of sight, and insight into melatonin's role in breast cancer? *Rev Assoc Med Bras* (1992). 2023;69(7):e697EDIT. <https://doi.org/10.1590/1806-9282.697EDIT>
- Stanojlović O, Šutulović N. Cirkadijalni sistem - mreža neurona sa suprahijazmatičnim jedrom na vrhu hijerarhijske organizacije. *Medicinski Podmladak*. 2018;69(3):3-13.
- Roa CL, Cipolla-Neto J, Reiter RJ, Linhares IM, Lepique AP, Aguiar LM, et al. Effects of melatonin alone or associated with acyclovir on the suppressive treatment of recurrent genital herpes: a prospective, randomized, and double-blind study. *Biomedicines*. 2023;11(4):1088. <https://doi.org/10.3390/biomedicines11041088>
- Veiga ECA, Simões RDS, Caviola LL, Abreu LC, Cavalli RC, Cipolla-Neto J, et al. Melatonin and the cardiovascular system in animals: systematic review and meta-analysis. *Clinics (Sao Paulo)*. 2021;76:e2863. <https://doi.org/10.6061/clinics/2021/e2863>
- Shiroma ME, Damous LL, Cotrim FP, Roa CL, Cipolla-Neto J, Reiter RJ, et al. Pretreatment with melatonin improves ovarian tissue cryopreservation for transplantation. *Reprod Biol Endocrinol*. 2021;19(1):17. <https://doi.org/10.1186/s12958-021-00705-4>
- Minguini IP, Luquetti CM, Baracat MCP, Maganhin CC, Nunes CO, Simões RS, et al. Melatonin effects on ovarian follicular cells: a systematic review. *Rev Assoc Med Bras* (1992). 2019;65(8):1122-7. <https://doi.org/10.1590/1806-9282.65.8.1122>
- Soares JM, Simões MJ, Oshima CT, Mora OA, Lima GR, Baracat EC. Pinealectomy changes rat ovarian interstitial cell morphology and decreases progesterone receptor expression. *Gynecol Endocrinol*. 2003;17(2):115-23. PMID: 12737672

10. Mayo JC, Sainz RM. Melatonin from an antioxidant to a classic hormone or a tissue factor: experimental and clinical aspects 2019. *Int J Mol Sci.* 2020;21(10):3645. <https://doi.org/10.3390/ijms21103645>
11. Farhood B, Goradel NH, Mortezaee K, Khanlarkhani N, Najafi M, Sahebkar A. Melatonin and cancer: from the promotion of genomic stability to use in cancer treatment. *J Cell Physiol.* 2019;234(5):5613-27. <https://doi.org/10.1002/jcp.27391>
12. Slominski RM, Reiter RJ, Schlabritz-Loutsevitch N, Ostrom RS, Slominski AT. Melatonin membrane receptors in peripheral tissues: distribution and functions. *Mol Cell Endocrinol.* 2012;351(2):152-66. <https://doi.org/10.1016/j.mce.2012.01.004>
13. Lin JD, Fang WF, Tang KT, Cheng CW. Effects of exogenous melatonin on clinical and pathological features of a human thyroglobulin-induced experimental autoimmune thyroiditis mouse model. *Sci Rep.* 2019;9(1):5886. <https://doi.org/10.1038/s41598-019-42442-0>
14. Sengul I, Sengul D, Pelikán A. Iodine-induced hyperthyroidism: do you mind? *Sanamed.* 2020;15(2):215-7. <https://doi.org/10.24125/sanamed.v15i2.458>
15. Iwan P, Stepniak J, Karbownik-Lewinska M. Pro-oxidative effect of KIO<sub>3</sub> and protective effect of melatonin in the thyroid-comparison to other tissues. *Life (Basel).* 2021;11(6):592. <https://doi.org/10.3390/life11060592>
16. Sengul I, Sengul D. Delicate needle with the finest gauge for a butterfly gland, the thyroid: is it worth mentioning? *Sanamed.* 2021;16(2):173-4. <https://doi.org/10.24125/sanamed.v16i2.515>
17. Sengul D, Sengul I, Soares Junior JM. Repercussion of thyroid dysfunctions in thyroidology on the reproductive system: conditio sine qua non? *Rev Assoc Med Bras (1992).* 2022;68(6):721-2. <https://doi.org/10.1590/1806-9282.20220255>
18. Todorovic J, Dugalic S, Sengul D, Stanisavljevic D, Detanac DA, Sengul I, et al. Revisiting type II diabetes mellitus in pregnancy and pregnancy outcomes such as in thyroidology: do you mind? *Rev Assoc Med Bras (1992).* 2023;69(3):447-51. <https://doi.org/10.1590/1806-9282.20221371>
19. Sengul D, Sengul I. Reassessing combining real-time elastography with fine-needle aspiration biopsy to identify malignant thyroid nodules. *Am J Med Case Rep.* 2021;9(11):552-3. <https://doi.org/10.12691/ajmcr-9-11-9>
20. Aras S, Tanzer İO, Can Ü, Sümer E, Baydili KN. The role of melatonin on acute thyroid damage induced by high dose rate X-ray in head and neck radiotherapy. *Radiat Phys Chem.* 2021;179:109206. <https://doi.org/10.1016/j.radphyschem.2020.109206>
21. Carlomagno G, Minini M, Tilotta M, Unfer V. From implantation to birth: insight into molecular melatonin functions. *Int J Mol Sci.* 2018;19(9):2802. <https://doi.org/10.3390/ijms19092802>
22. Olcese JM. Melatonin and female reproduction: an expanding universe. *Front Endocrinol (Lausanne).* 2020;11:85. <https://doi.org/10.3389/fendo.2020.00085>
23. Yi M, Wang S, Wu T, Zhang X, Jiang L, Fang X. Effects of exogenous melatonin on sleep quality and menopausal symptoms in menopausal women: a systematic review and meta-analysis of randomized controlled trials. *Menopause.* 2021;28(6):717-25. <https://doi.org/10.1097/GME.0000000000001757>
24. Treister-Goltzman Y, Peleg R. Melatonin and the health of menopausal women: a systematic review. *J Pineal Res.* 2021;71(2):e12743. <https://doi.org/10.1111/jpi.12743>

