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Melatonin: More Than Just the Hormone That Regulates Sleep

Melatonin is a hormone produced in the pineal gland, retina, GI tract, and white blood cells that is associated with sleep. In addition, there are melatonin receptors expressed all over the body, for example, in the intestines, fat tissue, kidneys, liver, lungs, adrenals, and other organs. The amount of melatonin the body produces decreases as one ages and depends on the activity of an enzyme called serotonin-N-acetyltransferase (NAT). The body's production of NAT, on the other hand, depends on its storage of vitamin B6.

Our Feature Article

Functions of Melatonin[1-5]

- Affects the release of sex hormones
- Aids the immune system
- Acts as an antioxidant
- Blocks estrogen from binding to receptor sites
- Decreases cortisol levels that are elevated
- Helps balance the stress response

- Helps prevent cancer and treat some cancers
- Improves mood
- Improves sleep quality
- Stimulates the parathyroid gland
- Stimulates the production of growth hormone
- Is cardioprotective
- Decreases platelet stickiness (decreases the risk of heart disease)
- Promotes healthy cholesterol levels
- Regulates skin pigmentation
- Relieves jet lag
- Dilates and contracts blood vessels
- Inhibits the release of prolactin, follicle stimulating hormone (FSH), and luteinizing hormone (LH)
- Inhibits the release of insulin from beta cells in the pancreas
- Protects skin cells against UV damage

Signs and Symptoms of Melatonin Deficiency

- Insomnia
- Fatigue
- Anxiety
- Early morning awakening
- Interrupted sleep

- Stress
- Increased risk of cancer
- Seasonal affective disorder
- Immunological disorders
- Heart disease
- Compromised immune system

Causes of Melatonin Deficiency

There are many etiologies of melatonin deficiency. Perhaps the most common cause of melatonin deficiency in today's world is electromagnetic fields. Other causes include the following:

- Acetaminophen
- Alcohol abuse
- Medications: alprazolam, atenolol, benserazide, bepridil, clonidine, dexamethasone, diazepam, diltiazem, felodipine, flunitrazepam, fluoxetine, isradipine, luzindole, metoprolol, nicardipine, nifedipine, nimodipine, nisoldipine, nitrendipine, prazosin, propranolol, reserpine, ronidazole (this list is not exhaustive)
- Tobacco
- High glycemic index foods

- Aspirin/indomethacin/ibuprofen
- Caffeine abuse
- Vitamin B12 deficiency

Therapeutic Benefits

The therapeutic benefits of melatonin are numerous. Melatonin is a hormone that does more than regulate the sleep cycle.

Hypertension. Melatonin has been shown to decrease blood pressure in patients with hypertension.[6-7] In fact, a study revealed that evening controlled-release melatonin, 2 mg for one month, significantly reduced nocturnal systolic blood pressure in patients with nocturnal hypertension.[8]

Heart Health. Patients with coronary artery disease tend to have low nocturnal serum melatonin levels. In addition, patients who developed adverse effects post myocardial infarction were shown to have lower nocturnal melatonin levels than patients without adverse effects. Melatonin is cardioprotective due to its vasodilator actions and free radical scavenger properties, and it also inhibits oxidation of LDL-C.[9-10] Likewise, melatonin has been shown to reduce hypoxia and prevent reoxygenation-induced damage in patients with cardiac ischemia and ischemic stroke.[11]

The MARIA study was a prospective, randomized, double-blind, placebo-controlled trial that used IV melatonin in patients following an acute MI that were having angioplasty. It decreased CRP and IL-6, two major markers of inflammation. Melatonin also attenuated tissue damage from reperfusion, decreased V tach and V fib after reperfusion, and reduced cellular and molecular damage from ischemia.[12] Another study revealed that there is an inverse correlation between melatonin levels and CRP levels after acute MI.[13] Moreover, melatonin has been shown to protect cardiac myocyte mitochondria after doxorubicin use.[14]

Insulin Regulation and Obesity. Melatonin is necessary for the proper synthesis, secretion, and action of insulin. In addition, melatonin acts by regulating GLUT4 expression, via its G-protein-coupled membrane receptors, the phosphorylation of the insulin receptor, and its intracellular substrates that mobilize the insulin-signaling pathway. Furthermore, melatonin is responsible for the establishment of adequate energy balance by regulating energy flow and expenditure through the activation of brown adipose tissue and participating in the browning process of white adipose tissue. Likewise, melatonin is a powerful chronobiotic, meaning that it helps regulate the body's internal clock. Consequently, the reduction in melatonin production that may occur with aging, shift work, or illuminated environments during the night commonly induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian changes that commonly lead to weight gain.[15] A study using laboratory animals

showed that melatonin supplementation daily at middle age decreased abdominal fat and lowered plasma insulin to youthful levels.[16] A low melatonin level is a frequently overlooked cause for an individual's inability to effectively lose weight.

Neurodegenerative Disorders. Studies have shown that low melatonin levels are associated with an increased risk of developing neurodegenerative diseases.[17-20]

Alzheimer's Disease. Some of the symptoms of low melatonin levels are also common to patients with Alzheimer's disease: disruption of the circadian rhythm of the body, mood changes, and delirium.[21-22] One medical trial showed that melatonin levels in the cerebrospinal fluid (CSF) in patients over the age of 80 were one-half the level of younger, healthier patients. Individuals in this study with Alzheimer's disease had even lower levels, only 20% of the amount observed in young healthy people.[23] Fortunately, numerous studies have shown that supplementing with melatonin helps to protect against Alzheimer's disease.[24-30] In addition, in animal and human trials a benefit in melatonin replacement in patients with early Alzheimer's disease was seen, even before it was clinically evident.[31-32] In fact, when melatonin was replaced early, the participants did not show pathological changes nor have symptoms of cognitive decline.[33] In addition, melatonin supplementation has been shown to decrease the damage caused by amyloid beta proteins and tau proteins.[34-38] Moreover, medical trials revealed that using melatonin in patients with Alzheimer's disease that they had better sleep patterns, less sundowning, and slower progression of cognitive loss.[39] Likewise, melatonin has also been shown to guard against the harmful effects of aluminum, which has been shown to cause oxidative changes in the brain that are similar to those seen in Alzheimer's disease.[40-41]

Mild Cognitive Impairment. Mild cognitive impairment (MCI) is impairment that precedes actual dementia.[42] In fact, 12% of people with MCI proceed to develop dementia each year.[43] Studies have shown that people who supplemented with melatonin (3-24 mg daily) for 15-60 months did much better on cognitive tests.[44-46]

Longevity. Lab trials have shown that melatonin replacement increases SIRT1, which is a longevity protein. SIRT1 is also activated by caloric restriction.[47]

Parkinson's Disease. Melatonin replacement has been shown to decrease the risk of developing Parkinson's disease.[48-50] In fact, animal trials have shown that melatonin can prevent and to some extent may even help reverse the motor and behavior changes that are associated with this disease process.[51-53]

In Parkinson's disease there is an accumulation of a protein called alpha-synuclein.[54] Melatonin supplementation also attacks alpha-synuclein and makes it more available to be removed by the body.[55-56] In addition, a lab study showed that melatonin can reverse the inflammatory changes that occur in Parkinson's disease.[57] Moreover, an animal trial also showed that melatonin helps to restore the normal activity of a key enzyme that is involved in the synthesis of dopamine.[58-59] Furthermore, in lab studies melatonin supplementation was shown to increase the survival of

dopamine-producing cells.[60-62] Consequently, more research needs to be done concerning melatonin's use in Parkinson's disease.

Cerebral Vascular Accident (CVA). If the patient has a low melatonin level, they have an increased risk of developing a stroke. The odds rise more than 2% for every 1 pg/mL decline in melatonin.[63] In fact, in individuals with a calcified pineal gland, the risk of developing a CVA is increased by 35%.[64] Moreover, melatonin supplementation has been shown to shrink the size of an infarct area in a patient with acute CVA. This may be due to melatonin's ability to neutralize free radical production.[65-70] Melatonin may also decrease the risk of CVA by significantly lowering cholesterol and also decreasing blood pressure.[71] Furthermore, melatonin supplementation in lab animals decreased the damage after stroke and decreased seizure occurrence.[72] In addition, melatonin has been shown to increase plasticity of neurons after CVA.[73] Likewise, in animal studies, melatonin reduced the damage caused by stroke by decreasing the activation of "protein-melting" enzymes.[74-75] Melatonin has also been shown to tighten the blood-brain barrier, reduce tissue swelling, and prevent hemorrhagic transformation in animal trials with experimentally induced stroke.[76-79]

Closed Head Injury (CHI)/Traumatic Brain Injury (TBI). Supplementation with melatonin has been shown to minimize the brain swelling and dysfunction that occurs after a closed head injury.[80-85] Melatonin supplementation has also been shown to help protect the brain in the case of traumatic brain injury.[86-87] Likewise, studies employing lab animals have shown that giving melatonin after a TBI had the following results: maintained the integrity of the blood-brain barrier, prevented dangerous brain swelling in the hours and days after injury, and shrank the size of the bruised and injured tissue.[88] Melatonin, likewise, reduced the mortality rate after burst aneurysm in laboratory studies.[89-90]

Sleep Hygiene. Melatonin has long been known to be beneficial for sleep. Melatonin has been shown to synchronize the circadian rhythms and improve the onset, duration, and quality of sleep. The good news is that exogenous melatonin supplementation is well tolerated and has no obvious short- or long-term adverse effects when used in small doses to improve sleep hygiene.[91-92]

Pre-Op Anxiety. When compared to placebo, melatonin given as premedication (tablets or sublingually) can reduce preoperative anxiety in adults. In fact, melatonin may be equally as effective as the standard treatment with midazolam in reducing preoperative anxiety. The effect of melatonin on postoperative anxiety in adults is mixed but suggests an overall attenuation of the effect compared to preoperatively.[93]

COVID-19. Melatonin is now being used as an adjuvant treatment for COVID-19 since it has been shown to limit virus-related diseases. It has also been demonstrated to be protective against acute lung injury and adult respiratory distress syndrome caused by viruses and other pathogens due to its anti-inflammatory and anti-oxidative effects.[94-96] Unfortunately, COVID-19 tends to take a more severe course in individuals with chronic metabolic diseases such as obesity, diabetes mellitus, and hypertension. Since COVID-19 complications frequently involve severe inflammation and oxidative stress in this population, melatonin is being suggested as an add-on therapy for patients that are diabetic and overweight.[97]

Cancer. Many studies have shown that melatonin is an effective therapy for breast cancer as an adjunct to traditional care.[98-102] It has also been shown to be effective for the prevention and reduction of some of the side effects of chemotherapy and radiation including mouth ulcers, dry mouth, weight loss, nerve pain, weakness, and

thrombocytopenia (low platelet count).[103] Moreover, melatonin has been used as a therapy for other cancer forms such as brain, lung, prostate, head and neck, and gastrointestinal cancer.[104]

Immune Builder. Melatonin has been shown to be a major regulator of the immune system. Consequently, disease states affecting a wide range of organ systems have been reported as benefiting from melatonin administration.[105-106]

Gastrointestinal Diseases. The enterochromaffin cells of the gastrointestinal tract secrete 400 times as much melatonin as the pineal gland. Consequently, it is not surprising that numerous studies have found that melatonin plays an important role in GI functioning. As previously mentioned, melatonin is a powerful antioxidant that resists oxidative stress due to its capacity to directly scavenge reactive species, increase the activities of antioxidant enzymes, and to stimulate the innate immune response through its direct and indirect actions. In the gastrointestinal tract, the activities of melatonin are mediated by melatonin receptors, serotonin, and cholecystokinin B receptors, as well as, via receptor-independent processes.[107-109]

Melatonin and the GI Tract

Let us now examine the use of melatonin in several disease processes of the GI tract. The prevalence of gastroesophageal reflux disease (GERD) is increasing with individuals experiencing symptoms such as heartburn, regurgitation, dysphagia, coughing, hoarseness, or chest pain. Fortunately, melatonin has been shown to have inhibitory activities on gastric acid secretion and nitric oxide biosynthesis. Nitric oxide has an important role in transient lower esophageal sphincter relaxation, which is a major etiology of reflux in people with this disease process. A study revealed that a combination of melatonin, l-tryptophan, vitamin B6, folic acid, vitamin B12, methionine and betaine was beneficial for patients with GERD. In addition, the other components of the formula exhibit anti-inflammatory and analgesic effects. All patients that took the combination of nutrients and melatonin reported a complete regression of symptoms after 40 days of treatment. However, only 65.7% of the omeprazole reported regression of symptoms in the same period.[110] Numerous other studies have also revealed that melatonin has a role in the improvement of gastro-esophageal reflux disease when used alone or in combination with omeprazole.[111-112]

In addition, melatonin can protect the GI mucosa from ulceration by its antioxidant action, stimulation of the immune system, limitation of gastric mucosal injury, and promoting epithelial regeneration. Melatonin can also reduce the secretion of pepsin and hydrochloric acid and influence the activity of the myoelectric complexes of the gut via its action in the central nervous system.[113-116] This hormone furthermore attenuates acute gastric lesions and accelerates ulcer healing via its interaction with melatonin receptors due to an enhancement of the gastric microcirculation.[117]

Similarly, melatonin is a promising therapeutic agent for irritable bowel syndrome (IBS) with activities independent of its effects on sleep, anxiety, or depression due to its important role in gastrointestinal physiology. It regulates gastrointestinal motility, has local anti-inflammatory reaction, as well as moderates visceral sensation. Studies have

consistently showed improvement in abdominal pain; some trials even revealed improvement in quality of life in these individuals.[118-121] In fact, studies have regularly publicized that alteration of the circadian rhythm is associated with the development of digestive pathologies that are linked to dysmotility or changes in microbiota composition in irritable bowel syndrome and similar conditions.[122-123]

Moreover, disruption of circadian physiology, due to sleep disturbance or shift work, may result in various gastrointestinal diseases, such as irritable bowel syndrome, gastroesophageal reflux disease, or peptic ulcer disease. In addition, circadian disruption accelerates aging and promotes tumorigenesis in the liver and GI tract. Furthermore, identification of the role that melatonin plays in the regulation of circadian rhythm allows researchers and clinicians to approach gastrointestinal diseases from a chronobiological perspective. Recently, it has been postulated that disruption of circadian regulation may lead to obesity by shifting food intake schedules.[124-125] Likewise, a study suggests that sensing of bacteria through toll-like receptor 4 (TLR4) and regulation of bacteria through altered goblet cells and antimicrobial peptides is involved in the anti-colitic effects of melatonin. Consequently, melatonin may have use in therapeutics for inflammatory bowel disease.[126]

Lastly, foods that are high in melatonin (phytomelatonin) have recently been shown to be considered important in preventing diseases of the liver. Currently, more studies are needed to examine the potential beneficial effects of supplemental melatonin, and foods rich in melatonin, in liver diseases and to better clarify the molecular mechanisms of action.[127]

Other Sources of Melatonin

The following are common foods that contain the most melatonin.

- Tart cherries
- Walnuts
- Corn
- Rice
- Peanuts
- Barley
- Oats
- Asparagus
- Tomatoes
- Black tea/green tea
- Broccoli
- Pomegranate
- Strawberries
- Brussels sprouts
- Black olives/green olives
- Cucumber
- Red grapes
- Mushrooms

Side Effects and Contraindications

Melatonin is an immune stimulator. Therefore, it should be used with caution in patients that have an autoimmune disease and individuals who are pregnant, breastfeeding, taking steroids, or who have a mental illness, leukemia, or lymphoma.

Signs and Symptoms of Elevated Levels

- Daytime sleepiness/fatigue
- Depression
- Headaches
- Increase in cortisol
- Intense dreaming/nightmares
- Suppression of serotonin

The most common reason that a person has an elevated level of melatonin is that they take too

large a dose or take melatonin and they do not need it. Likewise, an individual may also have high levels of melatonin if they eat too many foods that contain melatonin. Some medications such as clorgiline, desipramine, fluvoxamine, thorazine, tranylcypromine, and others may also raise melatonin levels as can St. John's wort supplementation. The herb Vitex agnus-castus (chaste tree) can also elevate melatonin levels. If melatonin levels are high, serotonin levels tend to decline. Therefore, it is very important to measure melatonin levels, by salivary testing, if taking more than one mg of melatonin at night.

Melatonin Dosing Schedules

Generally, women are more sensitive to melatonin than men if melatonin is being suggested for insomnia. Some women may need only a very low dose, and hence the melatonin may need to be compounded. In addition, medical studies have also suggested that as patients age, they may need less melatonin for insomnia.[128-130] As previously mentioned, large doses of melatonin are used to treat breast cancer and other cancers. Likewise, very large doses of melatonin are now being employed as co-therapies for COVID-19.[131] Measuring melatonin levels by salivary testing, before and after implementing melatonin therapy, for patients who are not hospitalized for COVID is recommended. For patients who are hospitalized for COVID, no testing methods have yet been standardized.

The following are common dosage ranges for patients. Changes in dosing may need to be employed depending on the results of follow-up salivary testing.

- Females under the age of 55: 0.25 to 1 mg, 30-60 minutes before bedtime
- Males under the age of 55: 1-3 mg, 30-60 minutes before bedtime
- Patients over the age of 55: In middle-age to older adults, the use of the lowest possible dose of immediate-release melatonin to best mimic the normal physiological circadian rhythm of melatonin and to avoid supra-physiological levels is suggested: 0.25 mg to 1 mg, 30-60 minutes before bedtime is commonly an adequate dose. Doses above 5 mg are not initially suggested for insomnia in patients over the age of 55.
- Cancer therapies: 12-20 mg, 30-60 minutes before bedtime
- COVID-19 as an adjunct therapy to other treatments:[132]
  - Patients with comorbidities: 3 to 10 mg, 30-60 minutes before bedtime
  - Health care workers with direct contact with COVID patients: 20 to 40 mg, 30-60 minutes before bedtime
  - Mildly symptomatic patients admitted on the hospital floor: 50 mg BID for 7 days
  - Patients admitted to the ICU: 200 mg BID for 7 days
  - **Review the medical literature before beginning therapy to check the newest recommendations since COVID-19 treatments are changing on a regular basis.**

Conclusion

Melatonin is a wonderful hormone that has so many functions in the body aside from regulating sleep. As you have seen, it has been shown to be an effective therapy for many disease processes along with a beneficial method to build the immune system.

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