

Melatonin and its use in atherosclerosis and dyslipidemia

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Abstract: A review of pineal melatonin synthesis, regulation, and physiological effects indicates that not only does melatonin act as a hormonal signal of darkness, but also that it possesses antioxidant and anti-inflammatory properties. Although oxidation and inflammation play a pivotal role in atherogenesis, no studies have investigated administration of melatonin for human arterial atherosclerosis. However, 13 clinical trials have investigated use of melatonin in dyslipidemia, which is a close correlate of atherosclerosis. The results of these clinical trials, particularly the five that are placebo-controlled, are inconclusive as to whether melatonin can normalize the blood lipid profile. Significant confounders in these studies might be a phase shift of the cholesterol rhythm by melatonin, a posture effect at venipuncture, uncontrolled diet during the course of melatonin intake, and the phenomenon of regression to the mean. Thus, future studies are required, which should also consider use of higher doses of melatonin and/or measurement of oxidized forms of cholesterol-containing particles (which are the most aggressive in relation to atherogenesis) in addition to lipidic fractions.

Keywords: melatonin, serum lipids, atherosclerosis, clinical trials

Introduction

This review addresses questions about melatonin which have arisen in discussions with clinicians and nonspecialists. In particular, it addresses the issue of whether melatonin is indeed protective against atherosclerosis, by reviewing the available clinical studies. This review is written primarily for clinicians, and was originally published in a local Russian journal in June 2012.¹ However, it has been extended to include four additional clinical trials, a summary table, and revised references (usually an initial hallmark publication and/or a review publication with the most comprehensive list of references on the topic).

Melatonin content in the human body

Melatonin is a small molecule that is synthesized consecutively from the essential amino acids tryptophan and serotonin.² To some extent, melatonin and serotonin are antagonists, eg, serotonin can provoke vasoconstriction whereas melatonin induces vasodilation. Melatonin is not to be biochemically mistaken for melanin, which is a melanophore pigment synthesized from tyrosine for protection of the body (in particular skin) against DNA damage by ultraviolet light. The hormone and pigment are linked functionally, and the name “melatonin” (ie, “melanophore-contracting hormone”) was given in 1958 by Lerner et al who first isolated the substance using a bioassay, whereby melatonin transiently lightens frog skin by inhibiting the darkening effect of

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hypophyseal melanocyte-stimulating hormone (intermedin).³ However, in higher order species, the melatonin-lightening effect is weakened; melatonin decreases melanin levels by lowering α -intermedin secretion in fur-producing animals, but has not been found to influence melanin content in humans.⁴

Melatonin is detectable in every human tissue and organ. The greatest content is in the gut, where it is synthesized for para-autocrine and autocrine action.^{5,6} The endocrine effect is due to its secretion into the bloodstream from the pineal gland (epiphysis), situated in the brain caudally from the hypothalamus and hypophysis. Melatonin secretion is the only known function of the pineal gland. Pineal melatonin is synthesized and released immediately during the dark period of the day in both diurnal and nocturnal animals, thereby acting as a biochemical transducer of day-night information in the body.⁷ Being soluble in lipids and water,^{8,9} and of small molecular weight, melatonin spreads rapidly into all fluids in the organism. During the daytime, there is practically no serotonin conversion into melatonin in the pineal gland. However, night-time elevation of melatonin in body fluids is not necessarily accompanied by its increase in cells.¹⁰

Melatonin is contained in many foods, predominantly those of plant origin, eg, cereals, grapes, and tomatoes¹¹ (see summary table in the paper by Bonnefont-Rousselot and Collin).¹² The highest levels (up to 13 ng/g) have been found in a variety of cherry.¹³ In cow's milk in winter, the amount is not very high, up to 0.03 ng/mL,¹⁴ and in beer is approximately 0.1 ng/mL.¹⁵ In order to attain a significant increase of melatonin in the blood, one should consume, according to calculations, about 1 kg of cherries, which corresponds to a melatonin intake of 13 μ g. This would increase its concentration in the blood up to 40 pg/mL (in comparison with normal night-time values of 25–80 (up to 200) pg/mL compared with daytime values < 3 pg/mL).¹⁶ In fact, cherry concentrate, containing 85 μ g of melatonin, increased 6-sulphatoxymelatonin levels in urine by 17%.¹⁷ Drinking 400 mL per day of a “stabilized” grape juice also elevated the 6-sulphatoxymelatonin concentration in urine.¹⁸ Serum melatonin is rapidly hydroxylated to 6-sulphatoxymelatonin in the liver, is excreted by the kidneys, and has a half-life of approximately 30 minutes.¹⁹

Regulation of melatonin secretion

Similar to hypothalamic neurohormones, melatonin secretion is exclusively neural-dependent. The polysynaptic pathway begins with the retinohypothalamic tract leading directly to the suprachiasmatic nuclei of the hypothalamus, descends

in the medial tract of the cervical cord, enters the superior cervical ganglion, returns to the spinal cord, and projects to the pineal gland. In persons with a transverse cut of the spinal cord at a cervical level (tetraplegia), melatonin secretion is absent (whereas secretion of thyrotropin and cortisol persists).²⁰ Some medications, especially some blockers of β_1 and α_1 adrenoreceptors, suppress melatonin secretion.²¹ In darkness or under dim ambient light (<10 lux, just sufficient to read freely), the 24-hour variations in melatonin secretion persist because the suprachiasmatic nuclei (the “biological clock”) exhibit genetically-based, endogenous circadian rhythms of neuronal activity (ie, pacemaker properties).²²

Light intensity of 10–100 lux (normal room level) acting via the eyes has some effect in suppressing nocturnal melatonin production, but higher levels are required to suppress it completely.^{23,24} This suppression is mediated by recently discovered melanopsin photoreceptors which are sensitive to blue light (wavelength about 480 nm, excitation), and which transmit impulses via the retinohypothalamic tract to the suprachiasmatic nuclei. These photoreceptors also transmit other biological effects of light, ie, shift of circadian rhythms, pupillary light reflex, and activation of the sympathetic nervous system,²⁵ with a partial contribution of retinal rods and cones to these so-called “nonvisual” effects of light. In vertebrates with thin cranial bones (birds, for example), melatonin suppression may occur due to a direct action of light on pinealocytes, because some of them retain similar opsin-based photopigments.²⁶

With the exception of light and some medications, no other interventions, including temperature, food intake, sleep, physical load, stress, or electromagnetic fields, impact significantly on melatonin secretion. A change in posture only nonspecifically influences the levels of melatonin, along with other substances in blood or saliva, changing the concentration by 10%–12% over 20 minutes, which is caused by redistribution of fluid between the interstitial space and the bloodstream.²⁷ Taking into account the steadiness and distinct nature of the circadian rhythm, measurement of melatonin in saliva or serum is considered to be the most reliable “hand” of the biological clock in humans.^{28,29} Endogenous and exogenous melatonin do not significantly influence central regulation of melatonin secretion levels,³⁰ despite the fact that the retina and suprachiasmatic nuclei contain a high concentration of melatonin receptors.³¹

Functions of melatonin

Nocturnally secreted melatonin, together with pulsatile surges of adrenocorticotrophic hormone secretion during the day,^{32–34} is considered to synchronize body physiology at the cellular

level, influencing expression of biological clock genes.³⁵ Synchronization to the 24-hour day, both internal (within the body) and external (to the light-dark cycle), is the major role of pineal melatonin in all species. Exogenous melatonin is thus used to minimize jet lag and synchronize other circadian rhythm disorders, particularly in blind subjects.³⁶ Another important role of melatonin is to transduce day length, thus signaling time of year in seasonal animals (reproduction, hibernation) and, to a lesser extent, in humans.^{37,38}

The other effect of melatonin, which is somewhat related to the regulation of circadian rhythmicity, is to promote sleep onset.^{39,40} One of the mechanisms involves a binding with melatonin receptors in arteriovenous anastomoses in the hands and feet, leading to capillary dilatation and heat loss, with a resulting decrease in core body temperature. Distal vasodilatation favors falling asleep.⁴¹ In contrast with many sleep medications, exogenous melatonin has little effect on sleep architecture, is almost lacking in side effects, and is recommended as a first-line medication for insomnia (in a prolonged-release form) in patients aged 55 years and older.⁴²

Melatonin significantly influences gonadotrophin and sexual function in animals⁴³ and may possibly play a role during puberty (eg, hypogonadism in children with melatonin hypersecretion due to a pineal tumor),⁴⁴ although little is otherwise known.^{45,46} Other properties of melatonin include a mild reduction in blood pressure,^{47,48} and antioxidative^{12,49,50} and anti-inflammatory^{51,52} effects; the latter two are considered to influence cancer growth and life span,^{53,54} and have a beneficial effect in several pathological conditions.⁵⁵

The absence of melatonin secretion is not a life-threatening state, in contrast with some other hormonal deficiencies. The amount of melatonin secreted diminishes with age because of a lowering of the mass and calcification of the pineal gland.⁵⁶ It is not the absolute amount of melatonin (which covers a wide range interindividually)^{57,58} but rather its decline in the individual that causes worse sleep⁵⁶ and probably other health-related problems. It has been shown experimentally that humans in modern society secrete 12.5% less melatonin because of use of artificial light in the early night.⁵⁹

Clinical effects of melatonin on atherosclerosis and lipids

Oxidation and inflammation are key components of atherogenesis.⁶⁰ Dyslipidemia is a well established risk factor for progression of atherosclerosis, with the risk being lower when blood levels of high-density lipoprotein (HDL) cholesterol are higher, and levels of low-density lipoprotein (LDL, “bad”) cholesterol and triglycerides are lower.⁶¹

When the total cholesterol level is above normal, it usually reflects increased levels of LDL cholesterol. Oxidized LDL particles play a significant role in atherogenesis.⁶⁰

Melatonin has antioxidative and anti-inflammatory properties.^{12,49–52} As distinct from such recognized endogenous antioxidants as β -carotene and vitamins E and C, melatonin does not undergo an enzymatic pathway of reduction after oxidation (redox cycling), but binds irreversibly to free radicals, and these compounds are removed by the kidneys. Not only melatonin but also precursors of its synthesis and products of its metabolism (eg, tryptophan, serotonin, 6-sulphatoxymelatonin) are able to reduce oxidative reactions, causing oxidative stress by direct free radical scavenging and indirect antioxidant activity. However, melatonin can be considered most favorable for use because of its ready passage into all cells, with excellent safety and tolerability.

A search for studies of the effects of melatonin on atherosclerosis and lipids was performed in the PubMed database (<http://www.pubmed.org>) using the key words “melatonin, atherosclerosis, human” and “melatonin, lipid, human”. References mentioned in relevant review articles were also considered. In addition, clinical studies of melatonin were searched for in the international register, <http://www.clinicaltrials.gov>.

Effect of melatonin on atherosclerosis

No studies were found of melatonin in the treatment of human atherosclerosis, and only three were found in animals. In two studies, supplementation of melatonin or its related compound, DTBHB (N-[2-(5-methoxy-1H-indol-3-yl)ethyl]-3,5-di-tert-butyl-4-hydroxybenzamide) to an atherogenic diet in mice with genetic hypercholesterolemia, compared with melatonin-free mice, led to a spreading or no significant change in atherosclerotic lesions of the aorta, despite clear inhibition of lipoprotein oxidation by these substances *in vitro*.^{62,63} The opposite was found in the third study, in that long-term intake of melatonin by genetically hypercholesterolemic rats hindered development of subendothelial fatty streaks formed by foam and mononuclear cells in the carotid artery, corresponding to an early stage of atherogenesis.⁶⁴

Effect of melatonin on lipids

Several animal studies have demonstrated an effect of melatonin on lipids. For example, an infusion of melatonin to genetically hypercholesterolemic rats decreased cholesterol levels in plasma and favored an involution of steatohepatosis,⁶⁵ although the cholesterol decrease may have been related to greater renal excretion.⁶⁶ In rats fed fructose,

which causes changes characteristic of the metabolic syndrome, melatonin attenuated deterioration of the lipid blood profile in a dose-dependent manner.⁶⁷ Two different dose levels of melatonin significantly decreased lipid peroxidation and levels of cholesterol, phospholipids, triglycerides, and free fatty acids in rat brain and liver.⁶⁸ In another study performed in normally fed rats, all lipid indices remained

unchanged, but there was an increase in long-chain n-6 polyunsaturated fatty acids in total plasma lipids and liver phospholipids.⁶⁴ More on the effects of melatonin on lipids in animals is summarized in a recent review.⁶⁹

Eight open-label clinical studies in humans were identified (Table 1). Melatonin was usually administered in the evening. Pittalis et al gave 10 mg melatonin for one month to 14

Table 1 Clinical studies of the effects of melatonin on lipids

Study	Subjects completed	Melatonin dose, time of day, and duration	Initial lipid levels	Results	Possible confounder
Open trials (no placebo control for melatonin)					
Pittalis et al ⁷⁰	14 patients with idiopathic hypercholesterolemia	10 mg "during the evening" for 1 month	TC > 200 mg/dL HDL and Tg – intermediate mean levels	HDL ↑ TC, Tg =	
Wakatsuki et al ^{71,72}	15 normolipidemic postmenopausal women	6 mg between 9 pm and 10 pm for 2 weeks	TC < 220 mg/dL Tg < 150 mg/dL LDL, HDL – optimal mean levels	VLDL, Tg, VLDL-Tg ↑ TC, LDL, HDL =	Regression to the mean
Pawlikowski et al ⁷³	14 elderly women	6 mg at 7 pm for 6 months	TC, LDL – intermediate, HDL, Tg – optimal mean levels	TC, LDL, HDL, Tg =	Circadian phase advance
Tamura et al ⁷⁴	10 perimenopausal and postmenopausal women	1 mg at 9 pm for 1 month	TC, LDL, HDL – intermediate, Tg – normal mean levels	HDL ↑ TC, LDL, Tg =	
Kadhim et al ⁷⁵	18 versus 15 type 2 diabetic patients receiving metformin	10 mg (+50 mg zinc acetate) versus placebo at bedtime for 3 months	TC, LDL – normal or higher, HDL – normal, Tg – higher versus healthy controls	TC, LDL, Tg ↓, HDL ↑	Regression to the mean
Koziróg et al ⁷⁶	30 subjects with metabolic syndrome	5 mg before bedtime for 2 months	TC, LDL, Tg – higher, HDL – lower versus healthy controls, intermediate mean levels	LDL ↓ TC, HDL, Tg =	Regression to the mean
Korkushko et al ⁷⁷	39 elderly versus 40 free-medicated elderly, with low melatonin levels	5 injections of epithalamin during a 15-day treatment course, and 6 courses of treatment half-yearly over 3 years	TC – unspecified LDL – high mean levels	TC, LDL ↓	
Shatilo et al ⁷⁸	30 elderly hypertensives	1.5–3 mg at 9 pm (+lisinopril or amlodipine) for 4 weeks	TC, LDL, HDL – intermediate, Tg – optimal mean levels	TC, LDL ↓ (in a subgroup with initially higher levels of TC) VLDL, HDL, Tg =	Regression to the mean
Placebo-controlled trials					
Rindone and Achacoso ⁷⁹	16 hypercholesterolemic patients; crossover study	0.3 mg, 3 mg, placebo at bedtime for 6 weeks each	LDL > 160 mg/dL TC, LDL, Tg – high, HDL – intermediate mean levels	TC, LDL, HDL, Tg =	
Seabra et al ⁸⁰	30 versus 10 healthy subjects	10 mg versus placebo 1 hour before bedtime for 1 month	TC, LDL, HDL – intermediate, Tg – optimal mean levels	TC, LDL, HDL, VLDL, Tg =	
Cichoz-Lach et al ⁸⁴	15 versus 15 patients with nonalcoholic fatty hepatosis	5 mg versus placebo twice daily (+Essentiale Forte*) for 1 month	TC – high-to-intermediate, LDL, Tg – high, HDL – low mean levels	Tg ↓ TC, LDL, HDL =	Regression to the mean
Gonciarz et al ^{82,83}	30 versus 12 patients with nonalcoholic fatty hepatosis	5 mg versus placebo at 9 am and 9 pm for 6 months + follow-up in 3 months	TC, Tg – intermediate-to-optimal mean levels	TC, Tg =	
Garfinkel et al ⁸¹	36 type 2 diabetic patients with insomnia; crossover study	2 mg (prolonged-release), placebo 2 hours before bedtime for 3 weeks each	Unspecified	TC, LDL, HDL, Tg =	

Notes: *Essentiale Forte, compound containing natural "essential" phospholipids (diglyceride esters of cholinephosphoric acid) enriched with unsaturated fatty acids, vitamins B1, B2, B6, B12, E, and nicotinamide.

Abbreviations: TC, total cholesterol (intermediate levels, 200–240 mg/dL); LDL, low-density lipoprotein cholesterol (100–160 mg/dL); HDL, high-density lipoprotein cholesterol (40–59 mg/dL for men, 50–60 mg/dL for women); Tg, triglycerides (150–200 mg/dL); VLDL, very-low-density lipoprotein cholesterol; =, no change; ↓, decrease; ↑, increase.

patients with idiopathic hypercholesterolemia and found an improvement in lipid concentrations, which were significant for HDL cholesterol.⁷⁰ In a study of 15 normolipidemic postmenopausal women who took 6 mg of melatonin for 2 weeks, triglyceride and very-LDL (VLDL) cholesterol levels deteriorated.^{71,72} In another group comprising 14 elderly women who took melatonin daily for 6 months, the serum lipid profile did not change.⁷³ In a fourth study, 10 perimenopausal and postmenopausal women received 1 mg of melatonin for a month, and an elevation of HDL cholesterol was observed.⁷⁴ In a fifth study, 33 patients with type 2 diabetes showed improvement in their lipid profile after 3 months of treatment with melatonin and zinc acetate compared with placebo,⁷⁵ but whether this was due to melatonin alone is not clear. In a sixth study, LDL cholesterol levels decreased following 2 months of treatment with melatonin in 30 subjects with metabolic syndrome, together with an improvement in the antioxidant properties of blood *in vitro*.⁷⁶ In a seventh study, six courses of intramuscular injections of the pineal extract, epithalamin, given at a 6-monthly interval over 3 years, resulted in an increased night-time plasma concentration of melatonin, a decrease in total and LDL cholesterol, and a deceleration of cardiovascular aging in 39 elderly subjects as compared with 40 controls.⁷⁷ In an eighth study of elderly hypertensives with increased total cholesterol levels, both total and LDL cholesterol levels were reduced following 2 or 4 weeks of melatonin administration at 9 pm.⁷⁸ However, this result might have been attributable to the regression towards the mean phenomenon (see below).

Five placebo-controlled clinical studies were identified (Table 1). In four studies, no change in the blood lipid profile was found. According to Rindone and Achacoso, there was no change in the lipid profiles of 16 subjects with hypercholesterolemia following administration of placebo, melatonin 0.3 mg, or melatonin 3 mg, each given in a random order.⁷⁹ A similar result was obtained in 30 healthy individuals after a month of taking melatonin 10 mg as compared with a group receiving placebo.⁸⁰ In 36 patients with type 2 diabetes, intake of prolonged-release melatonin or placebo for 3 weeks did not change total, LDL, and HDL cholesterol, or triglyceride concentrations.⁸¹ In 30 patients with nonalcoholic fatty liver disease, treatment with melatonin for 6 months also had no effect on cholesterol and triglyceride levels, nor were these levels changed 3 months after discontinuation of melatonin, compared with a group of 12 patients receiving placebo.^{82,83} However, in another study of 15 patients with nonalcoholic steatohepatitis who took Essentiale Forte® (Aventis, Bridgewater, NJ) and melatonin for one month, there was a decrease in levels of triglycerides and anti-inflammatory cytokines, as

compared with 15 patients who received Essentiale Forte and placebo.⁸⁴

In addition, in a nonclinical study of the immediate effect of melatonin in football players, serum concentrations of triglycerides and peroxidized lipids were found to be lower following physical training if 6 mg of melatonin was taken in advance, compared with a placebo group.⁸⁵

Regression to the mean might confound the results of some open clinical studies. The regression to the mean phenomenon postulates that abnormal initial values tend to shift automatically towards the population norm at remeasurement, without any specific interventions. For example, a high mean cholesterol level of 6.98 mmol/L might be expected to decrease to 6.40 mmol/L on re-examination.⁸⁶ In fact, three of the eight open clinical studies, in which initial levels of total cholesterol, LDL cholesterol, and/or triglycerides were high (or higher than in control subjects),^{75,76,78} reported a decrease after treatment with melatonin (Table 1). In contrast, an unfavorable increase in triglycerides was reported for a study in which the concentration was initially low (optimal) according to inclusion criteria.^{71,72}

Placebo control is the gold standard in evidence-based medicine. The majority of the placebo-controlled studies showed no effect of melatonin on the lipid profile (Table 1). Only one of the five studies documented a change (a decrease in triglyceride levels),⁸⁴ but placebo was not adequately defined in the methods section of the paper (nor clarified via emails by the authors) to estimate the validity of this change.

Melatonin administered ≥ 2 hours before the normal bedtime may phase advance the circadian system.⁸⁷ If this is the case, cholesterol levels, which rise in the morning,⁸⁸ would appear higher on remeasurement at the same time in the morning, masking the possible beneficial effect of melatonin. A posture-confounding effect (mechanism described above) on serum lipid concentrations upon morning venipuncture should also be considered.⁸⁹ Further, the effect of melatonin on the lipid profile may be too modest to be revealed over the masking effect of diet, which was usually not controlled for in the clinical studies. The degree of oxidation of LDL particles would probably be a better index of the effect of melatonin than lipid concentrations.^{85,90,91} Further, it is likely that only very high supraphysiological doses of melatonin could demonstrate an antioxidant effect *in vivo*.¹⁰

Correlation between endogenous melatonin and lipids

In two studies, night-time melatonin levels were found to correlate positively with HDL cholesterol levels and negatively

with total and LDL cholesterol levels.^{74,92} However, a study by Masue et al did not reveal a significant correlation between the morning amount of urinary 6-sulfatoxymelatonin and plasma lipid concentrations in 181 women.⁹³ In 24 patients suffering from multiple sclerosis, a subgroup with low levels of nocturnal plasma melatonin had higher serum total cholesterol concentrations than those in a subgroup with normal plasma melatonin levels.⁹⁴ In 60 patients with acute myocardial infarction⁹⁰ and in 21 patients suffering from unstable angina,⁹¹ night-time melatonin levels were decreased compared with controls and associated with elevated oxidized serum LDL levels. The latter and similar studies (reviewed in Dominguez-Rodriguez et al)⁹⁵ triggered the design of two clinical studies of the efficacy of intravascular injections of melatonin during angioplasty for limitation of ischemia-reperfusion injury in patients with acute myocardial infarction (<http://www.clinicaltrials.gov>, NCT00640094 and NCT01172171).

Conclusion

No studies demonstrating an effect of melatonin on arterial atherosclerosis in humans have been found. There are studies of the influence of melatonin on the serum lipid profile (a close correlate of atherosclerosis), but the results are ambiguous, in that the majority of open trials (six of eight) reported improvement in lipid indices following treatment with melatonin, whereas the majority of placebo-controlled studies (four of five) found no significant effect. This ambiguity may be partly attributable to methodological limitations. Nevertheless, considering the antioxidative and anti-inflammatory properties of melatonin, and also correlations between levels of endogenous melatonin and lipids in the blood, further studies are warranted, given that oxidation and inflammation play a pivotal role in atherogenesis.

Acknowledgment

The authors thank Anna Wirz-Justice for her English editing and comments on the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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