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Hypothalamic and Adipose Tissue Dysfunction: A Risky Association for Obesity

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Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies

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Key Words

Melatonin · Metabolic syndrome · Inflammation · Diabetes · Obesity · Insulin signaling · Aging

Abstract

The metabolic syndrome (MS) is a collection of risk factors for cardiovascular disease, including obesity, hypertension, hyperinsulinemia, glucose intolerance and dyslipidemia. MS is associated with low-grade inflammation of the white adipose tissue, which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes. Adipocytes secrete proinflammatory cytokines as well as leptin and trigger a vicious circle which leads to additional weight gain largely as fat. The imbalance between inflammatory and anti-inflammatory signals is crucial to aging. Healthy aging can benefit from melatonin, a compound known to possess direct and indirect antioxidant properties, to have a significant protective effect on mitochondrial function, to enhance circadian rhythm amplitudes, to modulate the immune system and to exhibit neuroprotective actions. Melatonin levels decrease in the course of senescence and are more strongly reduced in diseases related to insulin resistance. This short review article analyzes the multiple protective actions of melatonin that are relevant to the attenuation of inflamma-

tory responses and progression of inflammaging and how melatonin is effective to curtail MS in animal models of hyperadiposity. The clinical data supporting the possible therapeutic use of melatonin in human MS are also reviewed. Since attention has been focused on the development of potent melatonin analogs with prolonged effects (ramelteon, agomelatine, tasimelteon, piromelatine) and in clinical trials these analogs were administered in doses considerably higher than those usually employed for melatonin, clinical trials on melatonin in the range of 50–100 mg/day are needed to further assess its therapeutic value in MS.

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Inflammaging and the Metabolic Syndrome

The metabolic syndrome (MS) is a collection of risk factors for cardiovascular disease, including obesity, hypertension, hyperinsulinemia, glucose intolerance and dyslipidemia. MS is a major clinical challenge with a prevalence of 15–30%, depending on the world region considered [1–3]. MS increases overall cardiovascular mortality by 1.5–2.5 times and, together with neurodegenerative disorders like Alzheimer's disease, it represents one of the two major public health problems nowadays [4].

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There is impressive information indicating that the obesity in MS is associated with low-grade inflammation of the white adipose tissue, which can subsequently lead to insulin resistance, impaired glucose tolerance and diabetes [5, 6]. Adipocytes actively secrete proinflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-1 β and IL-6 as well as leptin, and trigger a vicious circle which leads to additional weight gain largely as fat. Increased circulating levels of C-reactive protein and other inflammatory biomarkers also support the occurrence of inflammation in obesity [7, 8].

Several studies have shown that altered production of proinflammatory cytokines modulates adipocyte size and number through paracrine mechanisms that exert an important role in the regulation of fat mass [9–11]. The amount of proinflammatory molecules derived from adipose tissue in obese patients diminishes after weight loss [12]. Therefore, the fat cells are both a source as well as a target for TNF- α , IL-1 β and IL-6.

The imbalance between inflammatory and anti-inflammatory signals is also a hallmark of aging and contributes to its progression. The term ‘inflammaging’ was introduced to underscore the importance of inflammation in senescence and its role in the development of age-related diseases as MS [13–15]. The levels of inflammatory mediators typically increase with age, even in the absence of acute infection or physiological stress. Such stress leads to inflammatory damage of cellular components, including proteins, lipids and DNA, and contributes to the age-related decline in physiological functions particularly in neural, immune and endocrine cells that regulate homeostasis. Therefore, the functional losses observed during aging include a slowly progressing, persistent type of oxidative stress resulting from the increased production of reactive oxygen species and reactive nitrogen species, which is enhanced by damage to the mitochondria [16, 17].

An age-related proinflammatory tendency is mostly unavoidable because of thymic involution and extended germ exposure, which both lead to the exhaustion of various subforms and developmental stages of leukocytes (details in Hardeland [17]). However, considerable inter-individual differences exist in the velocity of these changes and the balance between proinflammatory and anti-inflammatory cytokines [17]. This may in part be due to genetic predispositions [18] as well as to histories of viral load [19], which contribute an immune risk profile (IRP) [20]. In some centenarians, either an ‘inverted IRP’ has been found or a combination of elevated pro- and anti-inflammatory cytokines, two conditions which are believed to represent protective phenotypes [21, 22]. On this

background, it has been concluded that an increased tendency to inflammatory responses may place limits on lifespan [22], and that a well-functioning immune system is the strongest predictor of human longevity and healthy aging [23–25]. Therefore, inflammaging is associated with a state of oxidative stress, defined as an excessive production of reactive oxygen species and reactive nitrogen species compared to the level of antioxidants that act in the natural defense systems. Among antioxidants, melatonin has a special place for its antioxidant and anti-inflammatory properties, and partly for its role as a metabolic regulator [26, 27]. As melatonin modulates many processes involved in obesity and related metabolic disorders, it could have a therapeutic benefit in the treatment of obesity.

Melatonin and Inflammaging

A role of melatonin in attenuating inflammaging and its progression has been especially discussed with regard to options of treatment under conditions of reduced endogenous melatonin levels. Melatonin is one of the hormones known to decline during aging and, even more in a number of age-related diseases, changes that have been particularly documented in humans [26–28]. Interindividual variations observed among elderly persons may be explained, to a certain extent, by differences in the acquisition of melatonin-reducing diseases and disorders. Among these pathological causes of melatonin reduction, neurodegenerative processes have been identified as well as MS-related changes. For instance, decreases in melatonin were observed in coronary heart disease/cardiac syndrome X [28–34] and in diabetes type 2 [35, 36]. In either case, the pathophysiological nexus to inflammation and obesity is well established. Additional evidence from polymorphisms of human melatonin receptor genes indicates that deviations in melatonergic signaling favor the development of prediabetic states, diabetes type 2, elevated cholesterol and coronary heart disease (see [28]). Moreover, insulin resistance was induced in mice by knocking out the melatonin receptor MT₁ [37] and also by pinealectomy [38, 39].

Counteractions of inflammaging by melatonin seem to occur at different levels. One of them concerns the correction of metabolic dysregulation (table 1), including the prevention of insulin resistance, an inflammation-promoting change and hallmark of MS [40–43]. Notably, melatonin was effective in suppressing insulin resistance in different models, tissues and methods of induction (table 1).

Table 1. Effects of melatonin in animal models of hyperadiposity

Observation	Ref.
In rats fed from weaning with a high-fat diet, melatonin decreased body weight gain, feed efficiency and plasma glucose, leptin and triglyceride levels	44
In middle-aged rats receiving a high-calorie liquid diet, melatonin reduced weight gain and plasma insulin and leptin levels	45
In high-fat diet-fed mice, melatonin improved insulin sensitivity and glucose tolerance	46
In ovariectomized rats, melatonin was effective in reducing obesity	47–49
In olanzapine-treated rats, melatonin was effective in reducing obesity	50
In gold fish, body weight gain and specific growth rate were reduced by melatonin treatment	51
Melatonin and its analog piromelatonin inhibited weight gain and improved insulin sensitivity in high-fat-fed rats	52
In high-fat-fed rats, melatonin attenuated body weight increase, the increase in plasma glucose, insulin, adiponectin, leptin, triglycerides and cholesterol levels, and counteracted disrupted 24-hour patterns	53
Melatonin reduced body weight gain, visceral adiposity, blood triglyceride and insulin levels, and thiobarbituric acid reactive substances under a high-calorie diet in rats	54
In young male Zucker diabetic fatty rats, melatonin treatment reduced mean weight gain without affecting food intake, decreased in a nonsignificant way blood pressure and improved dyslipidemia	55
Melatonin improved MS induced by high-fructose intake in rats without affecting food intake	56–59
Melatonin and its analog piromelatonin reduced blood pressure in spontaneously hypertensive rats	60
Melatonin prevented the development of MS in male rats exposed to different light/dark regimens	61
Melatonin attenuated high-fat diet-induced fatty liver disease in rats	62
Melatonin, given at the time of reperfusion, prevented ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats	63
Melatonin ameliorated low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats	64
Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats	65
Melatonin normalized clinical and biochemical parameters of mild inflammation in rats with diet-induced MS syndrome	66
Melatonin counteracted changes in the hypothalamic gene expression of signals regulating feeding behavior in high-fat-fed rats	67
Melatonin reduced obesity and restored adipokine patterns and metabolism in obese (ob/ob) mice	68

Although in these studies several regulatory pathways have been found to be modulated by melatonin treatment, the decisive effect at which the relevant routes converge is the reduced serine phosphorylation of IRS-1 (insulin receptor substrate 1), which has sometimes been accompanied by an upregulation of IRS-1 expression. The activated, tyrosine-phosphorylated insulin receptor is

known to activate IRS subforms, in particular IRS-1, by tyrosine phosphorylation, a process that is inhibited by serine 307 phosphorylation which causes interruption of insulin signaling [69]. Melatonin and the melatonergic agonist piromelatonin have been shown to reverse the blockade of this key step of insulin signal transduction [41, 43, 52]. Persistent insulin sensitivity has in recent

years gained a particular relevance to inflammaging of the brain, because insulin resistance was shown to represent an early sign of low-grade neuroinflammation in dementias, such as Alzheimer's disease, and to aggravate their progression (see [70]).

A further level of action concerns the avoidance of processes that favor or lead to inflammation. This comprises calcium overload, excessive nitric oxide release that results in the formation of peroxynitrite, peroxynitrite-derived free radicals ($\cdot\text{OH}$, $\text{CO}_3^{\cdot-}$, $\cdot\text{NO}_2$), and, finally, tyrosine nitration as well as mitochondrial dysfunction with its consequence of oxidative stress (summarized in [17, 27]). All these changes are known to initiate low-grade inflammation in various organs, which is relevant to aging progression and comprises, in the central nervous system, microglia activation and vicious cycles via overexcitation and damage by oxidants that ultimately cause impaired neuronal and astrocytic functions. In various animal models, melatonin has been shown to counteract these detrimental processes to a substantial extent, by multiple antiexcitatory actions [17, 71], mitochondrial protection [17, 27, 42, 72–74], reduction of peroxynitrite-related damage [75] and attenuation of microglia activation [27, 76, 77]. These effects go far beyond the frequently discussed direct antioxidant properties of melatonin based on scavenging of free oxygen radicals. In fact, antioxidative protection by melatonin comprises various mechanisms that reduce the formation of free radicals rather than eliminating those already formed, as outlined in the concept of radical avoidance [78].

Immunological effects of melatonin represent a third area relevant to inflammaging. In this field, one of the major problems consists of melatonin's multiple roles as an immune modulatory agent, which comprise both pro-inflammatory and anti-inflammatory actions, which, consequently, also lead to either a pro-oxidant or anti-oxidant balance [17, 27, 79]. At first glance, these observations appear to be contradictory, but they may only reflect the conditionality of melatonin's actions. However, the precise reasons for when melatonin behaves in a pro- or anti-inflammatory way remain to be identified, although the strength of inflammation and the temporal sequence of initiation and healing processes may play a role. Moreover, changes due to immune remodeling in the course of senescence have to be taken into account. With regard to aging and age-associated diseases, pro-inflammatory/pro-oxidant effects are mainly observed under rheumatic conditions, especially rheumatoid arthritis [80, 81]. However, under other conditions concerning senescence, melatonin's anti-inflammatory side seems to

prevail. In the liver of aged, ovariectomized female rats, melatonin downregulated proinflammatory cytokines, such as TNF- α , IL-1 β and IL-6, and upregulated the anti-inflammatory IL-10 [82]. Corresponding findings were obtained in the dentate gyrus, in conjunction with an up-regulation of sirtuin 1 [83], which is assumed to also possess anti-inflammatory properties. Reductions of TNF- α and IL-1 β and increased levels of IL-10 were also observed in the liver [84], pancreas [85] and heart [86] of the senescence-accelerated mouse strain SAMP8. Numerous other reports on anti-inflammatory actions of melatonin that were not obtained under conditions of aging, but in brain trauma, ischemia/reperfusion, hemorrhagic shock and various forms of high-grade inflammation including endotoxemia and sepsis, have been summarized elsewhere [17]. The applicability of these results to inflammaging and MS remains uncertain, but the data certainly underline melatonin's anti-inflammatory potential.

Melatonin-induced changes in gene expression require detailed analyses beyond the primary signaling pathways transduced by the MT₁ and MT₂ receptors via decreases in cAMP and ERK1/2 activation and modulations by protein-protein interactions [87]. However, from a mechanistic point of view, it is not always possible to discriminate between direct actions and indirect effects via changes in the phase and amplitude of circadian oscillators. While the changes induced in the circadian master clock, the suprachiasmatic nucleus (SCN), are relatively well understood, this is less the case in the numerous peripheral oscillators, which strongly differ in their dependence on the SCN [88]. Since circadian oscillators are cellular machineries, in which the core oscillators are modulated by accessory oscillator components in an often cell type-specific way [89, 90], tissue-dependent differences can be expected. With regard to the cellular generation of circadian rhythms, oscillators may be assumed to be present in any nucleated nonresting cell. Notably, peripheral oscillators exist in cells of particular relevance to MS, such as pancreatic β -cells [91], hepatocytes, adipocytes, cardiomyocytes [92] and leukocytes [93, 94]. Moreover, the effects of melatonin are known in all these cell types, and the factors involved in metabolic sensing are modulated by this hormone, such as peroxisome proliferator-activated receptor- γ coactivator-1 α (PGC-1 α), peroxisome proliferator-activated receptor- γ , phosphoinositide 3-kinase, protein kinase B (Akt), including the accessory oscillator components AMP kinase, nicotinamide phosphoribosyl transferase and sirtuin 1 [17, 90]. However, the effects of melatonin on all these factors are by far not uniform, but rather often contradictory or, at least, con-

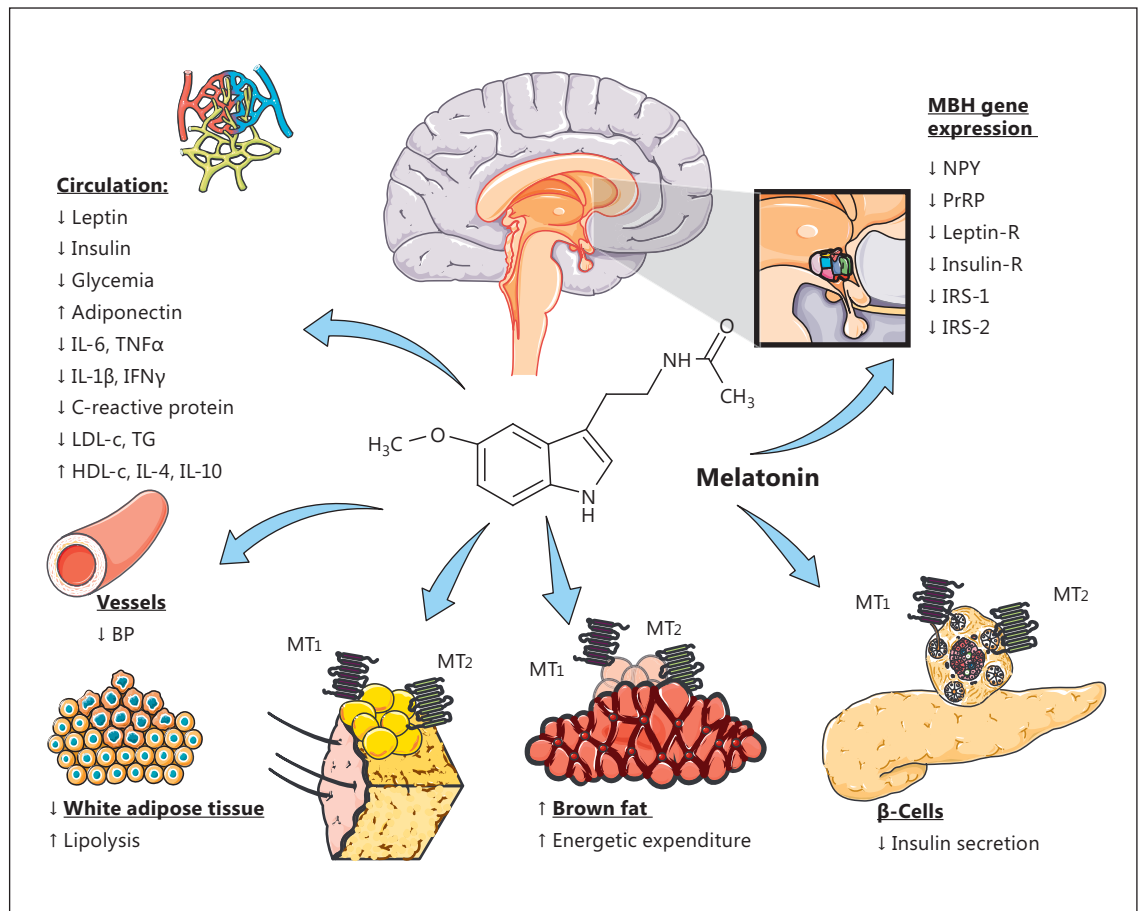


Fig. 1. In several animal models of MS, hyperadiposity occurs together with an augmented systolic blood pressure (BP), increased circulating low-density lipoprotein cholesterol (LDL-c), total cholesterol and triglyceride (TG) concentration, and proinflammatory cytokine levels. Melatonin injection is able to normalize most

observed alterations and corrects the altered biochemical proinflammatory profile (see table 1 for references). IFN γ = Interferon- γ ; HDL-c = high-density lipoprotein cholesterol; MBH = medial basal hypothalamus; NPY = neuropeptide Y; PrRP = prolactin-releasing peptide.

ditional [17]. Therefore, it is of utmost importance to remain in the context of inflammaging and to discriminate between direct effects and indirect actions via circadian central or peripheral oscillators, demands that frequently have not been considered in respective studies. It would also be important to be aware of the fundamental rules of phase dependency of any action on circadian oscillators, which can lead to either up- or downregulations at different circadian times. Cases of direct effects not mediated by oscillators may be present in the induction of antioxidant enzymes in the rat liver and pancreas under inflammatory conditions, where melatonin promotes the expression and nuclear translocation of nuclear factor erythroid 2-related factor 2 that mediates the upregulation of the protective enzymes [95–97]. Correspondingly,

melatonin reduced proinflammatory factors such as TNF- α , IL-1 β and inducible nitric oxide synthase by suppressing the expression of nuclear factor- κ B via recruitment of a histone deacetylase to its promoter [95, 96]. However, it is important to remain aware of the conditionality of melatonin effects on pro- and anti-inflammatory cytokines, which may be either up- or downregulated by this hormone [79]. Importantly, proinflammatory cytokines such as TNF- α , IL-1 β and IL-6 have been shown to be reduced in various models of aging, whereas the anti-inflammatory IL-10 was typically stimulated [27]. Whether this would be also the case under conditions of beginning MS at younger age deserves future attention and thorough analysis, especially as the proinflammatory cytokines are usually upregulated by melato-

nin under basal conditions [79]. Various other effects of melatonin on gene expression seem to be mediated by the circadian system. In particular, the role of SIRT1 should be considered, which is not only believed to be an aging suppressor; it acts as a protein deacetylase and, moreover, as a component of circadian oscillators that interacts with the BMAL1/CLOCK dimer and is required for high rhythm amplitudes [89, 98]. In various models of aging including senescence-accelerated mice, SIRT1 was up-regulated by melatonin and caused enhanced deacetylation of various of its substrates, such as PGC-1 α , FoxO1, NF κ B, and p53 [27, 86]. Notably, these effects strongly contrast with opposite effects in epigenetically dysregulated oscillators of cancer cells. Other aspects of epigenetic modulation including possible indirect effects by melatonin via circadian oscillators have recently been summarized [99].

Evidence of Melatonin's Therapeutic Value in MS: Animal Studies

Treatment with melatonin in rats has the ability to reduce obesity, type 2 diabetes and hepatic steatosis [100, 101]. In several animal models of hyperadiposity, melatonin injection was able to normalize most observed alterations and correct the altered biochemical proinflammatory profile (fig. 1; table 1).

Moreover, melatonin treatment of streptozotocin-induced type 1 diabetic rats induces the regeneration and proliferation of β -cells in the pancreas leading to a decrease in blood glucose [102]. Loss of melatonin in circulation after pinealectomy of rats results in hyperinsulinemia and accumulation of triglycerides in the liver [103]. The long-term administration of melatonin improves lipid metabolism in type 2 diabetic rats via restoring insulin sensitivity [104]. Melatonin treatment increases glycogen content in the liver of rats [105] and in high fat diet-induced diabetic mice the intraperitoneal injection of 10 mg/kg melatonin improved glucose utilization and insulin sensitivity and ameliorated hepatic steatosis [106].

Table 1 summarizes the effect of melatonin in animal models of obesity. Melatonin was usually very effective in reversing hyperadiposity. The reasons for the decrease in body weight after melatonin in the absence of significant differences in food intake are worth exploring. A key piece of evidence in this regard is the observation that melatonin plays a role in seasonal changes in adiposity by increasing the activity of the sympathetic nervous system innervating white fat which leads to lipolysis [107].

Melatonin not only affects white adipose tissue, but also increases the recruitment of brown adipocytes and increases their metabolic activity in mammals (see [108]). It has been speculated that the hypertrophic effect and functional activation of brown adipose tissue induced by melatonin can likely be applied to treatment of human obesity. Collectively, the results indicate that the administration of melatonin effectively counteracts some of the disrupting effects seen in diet-induced obesity in animals, in particular insulin resistance, dyslipidemia and obesity.

Evidence for Melatonin's Therapeutic Value in MS: Clinical Studies

Table 2 summarizes the results of clinical studies on melatonin's activity relevant to human MS. Medical literature was identified by searching databases (MEDLINE, Embase), including bibliographies from published literature and clinical trial registries/databases. Searches were last updated on March 23, 2016.

Type 2 diabetic patients have low circulating levels of melatonin [36] with a concurrent and expected upregulation of mRNA expression of melatonin membrane receptor [109]. Furthermore, allelic variants for melatonin receptors were associated with the level of fasting blood glucose and/or increased risk of type 2 diabetes [110–112] and with polycystic ovary syndrome [113]. These findings strongly bind melatonin to glucose homeostasis in blood.

Patients with coronary artery disease show decreased melatonin secretion [31–34], and among elderly hypertensive individuals, nocturnal urinary melatonin excretion was inversely associated with the nondipper pattern [114]. In turn, administered melatonin proved capable of reducing nocturnal blood pressure in hypertensives [117–120] and attenuated age-dependent disturbances of cardiovascular rhythms [121]. A meta-analysis of randomized controlled trials suggests that melatonin-controlled release is effective and safe in improving nocturnal hypertension [136]. As a pleiotropic molecule, melatonin may exert its antihypertensive and anti-remodeling effects through its antioxidant and scavenging properties, preserving the availability of nitric oxide and having sympathoplegic effects that provide cardiovascular protection in MS.

As well as in animal models, clinical studies have shown that melatonin improves lipid profiles in MS patients. Melatonin treatment (1 mg/kg for 30 days) increased the levels of high-density lipoprotein cholesterol

Table 2. Clinical observations on melatonin relevant to MS

Finding	Subjects	Design	Study duration	Treatment	Measured	Results	Ref.
Low plasma melatonin levels in type 2 diabetic patients	36 type 2 diabetic patients and 13 age-matched healthy subjects	Observational study	Unquoted	None	Serum melatonin levels measured by RIA between 02.00–04.00 and 16.00–18.00 h. Cardiovascular reflex tests, HRV, and 24-hour BP monitoring	Nocturnal melatonin levels and the nocturnal melatonin surge were significantly lower in the diabetic group. A negative correlation occurred between nocturnal melatonin levels and the degree of systolic BP decrease at night. Patients with autonomic neuropathy showed decreased melatonin levels both at night and during day when compared to healthy controls. In patients with autonomic neuropathy, nocturnal melatonin levels were positively correlated with nocturnal high- and low-frequency components of HRV and systolic and diastolic BP at night	36
Increased number of melatonin receptors in type 2 diabetic patients	Surgical specimens of pancreata obtained from 25 patients who underwent partial or total pancreatectomy because of cancer or severe chronic pancreatitis	Observational study	Unquoted	None	Real-time PCR and immunocytochemistry of MT ₁ and MT ₂ receptors	The existence of the melatonin MT ₁ and MT ₂ receptors in human pancreatic tissue and in islets of Langerhans was assessed. mRNA transcript levels of melatonin receptors and their immunocytochemical expression were significantly higher in type 2 diabetic patients. Transcripts of the nuclear orphan receptors were also higher in human pancreatic tissue and islets of type 2 diabetic patients	109
Melatonin receptor gene polymorphism associated with high risk of type 2 diabetes	36,610 individuals of European descent	Observational study	Unquoted	None	Leading association signals in ten genome-wide association scans	The strongest signal was observed at rs10830963, where each G allele (frequency 0.30 in HapMap CEU) was associated with an increase of 0.07 mmol/l in fasting glucose levels and reduced β -cell function as measured by homeostasis model assessment. The same allele was associated with an increased risk of type 2 diabetes	110
Genetics of MT ₂ receptor associated with left ventricular function in hypertensive patients	605 patients with arterial hypertension and cardiac ejection fraction \leq 40%	Observational study	Unquoted	None	SNPs of MT ₂ Cardiac parameters assessed by echocardiography	Analysis of SNPs rs10830962, rs4753426, rs12804291, rs10830963 and rs3781638 revealed two haplotypes, 1 and 2, with frequencies of 0.402 and 0.277, respectively. Carriers with haplotype 1 showed a higher mean 24-hour systolic BP. Haplotype 2 was significantly related to cardiac ejection fraction with an absolute increase of 1.8% in carriers vs. noncarriers	111
Genetics of MT ₂ receptor associated with increased risk of impaired fasting glucose in youth with obesity	346 Caucasians, 218 African-Americans, and 217 Hispanics, obese children and adolescents	Observational study	Variable	None	Oral glucose tolerance test. Evaluation of insulin secretion by the oral minimal model	The MTNR1B rs10830963 variant was associated with higher fasting glucose levels and lower dynamic β -cell response in Caucasians and Hispanics and conferred an increased risk of showing impaired fasting glucose on Caucasians, African-Americans and Hispanics	112
Melatonin receptor gene polymorphisms in polycystic ovary syndrome	789 participants (Han Chinese)	Observational study	Unquoted	Unquoted	Genotypes were obtained by sequencing	An association was detected between MTNR1B rs2119882 and polycystic ovary syndrome, suggesting that the MTNR gene may indicate increased susceptibility to polycystic ovary syndrome in Chinese. No significant association was found for rs10830963. CC genotype carriers had higher levels of clinical and metabolic features of polycystic ovary syndrome than the TC and TT genotypes. A significant difference in transmission of allele C of rs2119882 was found between obese and nonobese women with polycystic ovary syndrome	113
Low melatonin production in coronary disease independent of β -adrenoceptor blockade	48 male patients with angiographically documented severe coronary artery disease. 18 age-matched men, with no evidence of coronary sclerosis, served as controls	Observational cross-sectional study	Unquoted	24 patients took β -blockers daily in therapeutic dosages	aMT6s was measured by RIA from overnight urine	Primary aMT6s concentration was significantly decreased in patients, and β -blocker treatment did not suppress melatonin production further	31

Table 2 (continued)

Finding	Subjects	Design	Study duration	Treatment	Measured	Results	Ref.
Low melatonin production in coronary disease independent of β -adrenoceptor blockade	Three groups of individuals were studied: (a) 24 healthy subjects; (b) 32 patients with chronic, stable, coronary disease; (c) 27 patients with unstable angina	Observational cross-sectional study	Unquoted	24 patients with chronic coronary disease and 14 patients with unstable angina received β -blockers daily in therapeutic dosages	aMT6s was measured by RIA from overnight urine	Urinary aMT6s excretion was significantly lower in unstable angina patients than in healthy subjects or in patients with stable angina. aMT6s correlated negatively with age in healthy subjects, but not in coronary patients. aMT6s excretion in patients treated with β -adrenoceptor blockers did not differ significantly from coronary patients not receiving β -blockers	32
Low melatonin production in myocardial infarction	25 patients diagnosed with acute myocardial infarction, and 25 patients with no evidence of coronary artery disease were studied	Observational cross-sectional study	Unquoted	Unquoted	Levels of melatonin, glutathione peroxidase and lipid peroxidation in serum samples collected at 10.00 h (light period) and 03.00 h (dark period)	A reduced nocturnal elevation of melatonin was found in the acute myocardial infarction group. Glutathione peroxidase levels were lower after acute myocardial infarction and did not show diurnal variations. In the control group, lipid peroxidation levels presented a light/dark pattern, but in the acute myocardial infarction group diurnal variations of this parameter were lost	33
Low melatonin production in coronary disease	16 patients with angiographically documented coronary disease and 9 healthy controls	Observational cross-sectional study	Unquoted	Unquoted	Melatonin levels measured by RIA in serum samples collected every 2 h between 22.00 and 08.00 h	A large interindividual variation in the pattern of melatonin secretion was seen in both groups. Patients with coronary disease secreted less nocturnal melatonin at 02.00, 04.00 and 08.00 h than control subjects. Peak time of melatonin secretion was observed earlier in patients with coronary disease (02.00 vs. 03.45 h)	34
Low melatonin production in elderly hypertensives	141 elderly hypertensives	Observational cross-sectional study	Unquoted	Unquoted	Overnight urinary melatonin excretion, ambulatory blood pressure and actigraphic physical activity	When participants were divided into two groups (high- and low-melatonin groups) by the cutoff value for identifying the top tertile, the characteristics, except for age, did not significantly differ between the two groups. In a multivariate analysis after adjustment for age, diabetes and daytime activity, the odds ratio for the nondipper pattern in the high-melatonin group was significantly lower than that in the low-melatonin group. The mean percentage systolic blood pressure nocturnal fall, adjusted for the former covariates, was significantly higher in the high-melatonin group than the low melatonin group. Among elderly hypertensive individuals, nocturnal urinary melatonin excretion was significantly and inversely associated with the nondipper pattern	114
Melatonin treatment decreases nocturnal BP in type 1 adolescent diabetics	11 normotensive adolescents with type 1 diabetes and 10 healthy controls	Randomized placebo-controlled double-blind crossover study	2 weeks	5 mg melatonin or placebo taken at bedtime p.o.	BP every 20 min for 24 h by an ambulatory device on the day before and on the last day of each treatment. Sleep measures were recorded by a diary and a wrist activity meter	Exogenous melatonin given to healthy normotensive adults reduces BP. In the patients with type 1 diabetes, the decline in diastolic BP during sleep was significantly greater on melatonin than on placebo. No significant drug effect was present in the controls. No significant side effects were noted	115
Melatonin treatment decreased nocturnal BP in type 1 adolescent diabetics	9 normotensive adolescents with type 1 diabetes and 8 healthy controls	Open-label trial	1 week	10 mg melatonin taken at bedtime p.o.	BP was measured every 20 min by ambulatory monitoring device for 24 h before treatment onset and on the last treatment day; sleep was monitored by diary and wrist actigraphy	In patients with diabetes, the mean BP during sleep was lower on melatonin than before treatment. In controls, there was no significant effect of melatonin on BP. There was no significant effect of sleep duration or number of awakenings on the BP responses	116
Melatonin treatment decreased high nocturnal BP in hypertensives	16 men with untreated essential hypertension	Randomized placebo-controlled double-blind crossover study	3 weeks	Acute (single) and repeated (daily for 3 weeks) oral melatonin (2.5 mg) intake 1 h before sleep	BP was measured every 20 min by ambulatory monitoring device for 24 h before treatment onset and on the last treatment day	Repeated melatonin intake reduced systolic and diastolic BP during sleep by 6 and 4 mm Hg, respectively. The treatment did not affect the heart rate. The day-night amplitudes of the rhythms in systolic and diastolic BP were increased by 15 and 25%, respectively. A single dose of melatonin had no effect on BP. Repeated (but not acute) melatonin also improved sleep	117

Table 2 (continued)

Finding	Subjects	Design	Study duration	Treatment	Measured	Results	Ref.
Melatonin treatment decreased high nocturnal BP in hypertensives	18 women, 47–63 years of age with normal BP (n = 9) or treated essential hypertension (n = 9)	Randomized double-blind study	6 weeks	Slow-release melatonin pill (3 mg) or placebo 1 h before going to bed	Ambulatory BP was recorded for 41 h at baseline at the end of each treatment period	In comparison with placebo, melatonin administration did not influence diurnal BP but did significantly decrease nocturnal systolic, diastolic and mean BP without modifying the heart rate. The effect was inversely related to the day-night difference in BP	118
Melatonin treatment decreased high nocturnal BP in hypertensives	38 treated hypertensive patients with confirmed nocturnal hypertension according to repeated 24-hour ambulatory BP monitoring	Randomized double-blind study	4 weeks	controlled release melatonin 2 mg or placebo 2 h before bedtime	Ambulatory BP was recorded for 24 h	Melatonin treatment reduced nocturnal systolic BP significantly from 136 to 130 mm Hg, and diastolic BP from 72 to 69 mm Hg, whereas placebo had no effect on nocturnal BP. The reduction in nocturnal systolic BP was significantly greater with melatonin than with placebo and was most prominent between 02.00 and 05.00 h. Nocturnal BP control in treated patients with nocturnal hypertension	119
Melatonin treatment decreased high nocturnal BP in type 2 diabetic hypertensives	60 dipper and 64 nondipper patients	Open-label trial	8 weeks	3 mg melatonin p.o. at bedtime was administered to 32 dipper and 34 nondipper patients for 4 weeks. Then the same patients received 5 mg of melatonin for the next 4 weeks. 28 dippers and 30 nondippers did not receive melatonin	Ambulatory BP was recorded for 24 h	29.5% of nondippers treated with 3 mg/day melatonin achieved features of dippers compared to controls. 5 mg of melatonin per day restored normal diurnal BP rhythm in 32.4% of nondippers. In nondippers treated with melatonin, significant decreases in diastolic, systolic and mean night BP values were observed	120
Melatonin treatment attenuated age-dependent disturbances of cardiovascular rhythms	97 normotensive and hypertensive volunteers (63–91 years old)	Placebo-controlled trial	3 weeks	1.5 mg melatonin or placebo p.o. each day at 22.30 h for 2 weeks	Systolic and diastolic BP and HR were measured using semiautomated devices at 03.00, 08.00, 11.00, 14.00, 17.00, 23.00 h each day of the 1st and the 3rd week	The 24-hour HR rhythm was monophasic with a steeper increase in the morning. The daily systolic and diastolic BP rhythms were bimodal. In reference to previously reported data of younger subjects, mean BP was elevated, particularly the nocturnal fall was less pronounced. Also, the overall systolic BP variability was higher as was the percentage of the 12-hour component. Both values and also the systolic and diastolic BP were reduced during melatonin treatment. The hypotensive effect of melatonin was most pronounced between 03.00 and 08.00 h. Melatonin not only has a direct hypotensive effect, it also stabilizes the internal temporal order enhancing the circadian component and the synchronization between rhythms of different physiological functions	121
Melatonin treatment prevented catecholamine-induced hypercoagulability	45 healthy young men	Placebo-controlled trial	1 h	A single oral dose of either 3 mg melatonin (n = 24) or placebo (n = 21). One hour thereafter, they underwent a standardized short-term psychosocial stressor	Plasma levels of clotting factor VII activity (FVII:C), FVIII:C, fibrinogen, D-dimer, and catecholamines were measured at rest, immediately after stress, and 20 and 60 min after stress	Compared with the melatonin group, the placebo group showed a greater increase in absolute D-dimer levels from rest to immediately after stress and a significant recovery of D-dimer levels from immediately after stress to 60 min thereafter. Stress-induced changes in FVII:C, FVIII:C, fibrinogen, and catecholamines did not significantly differ between groups. Oral melatonin attenuated the stress-induced elevation in the sensitive coagulation activation marker D-dimer without affecting catecholamine activity	122
Melatonin inhibited human platelet aggregation	22 healthy young men	In vitro study	Unquoted	10^{-9} to 10^{-5} M melatonin	Platelet aggregation and TxB2 production in PRP	Melatonin inhibited in a dose-dependent way ADP-induced platelet aggregation with individual inhibitions 40% or more at 10^{-6} to 10^{-5} M concentrations and a higher global inhibition at 18.00 h. TxB2 production elicited by AA in the evening was inhibited significantly in a concentration-related manner by 10^{-9} to 10^{-5} M melatonin, while during the morning hours the inhibition was significant only at 10^{-6} M or higher melatonin concentrations. Melatonin depression of TxB2 generation was about 2-fold greater at 18.00 h than at 08.30 h	123

Table 2 (continued)

Finding	Subjects	Design	Study duration	Treatment	Measured	Results	Ref.
Melatonin inhibited human platelet aggregation	10 healthy young men and 5 women in early follicular phase	In vitro study	Unquoted	10^{-9} to 10^{-5} M melatonin	Platelet aggregation and ATP and serotonin release in PRP	ADP-induced ATP and serotonin release, indexes of platelet secretory processes, showed a generally greater, dose-dependent inhibition after adding melatonin (10^{-9} to 10^{-5} M concentrations) at 20,30 h as compared to 08,30 h	124
Melatonin inhibited human platelet aggregation	5 healthy young men	Observational study	Unquoted	For in vitro studies 10^{-9} to 10^{-5} M melatonin were used	Plasma melatonin concentration, platelet aggregation and Tx _{B2} production in PRP sampled at 2-hour intervals from 21.30 to 09.30 h	Inhibition by 10^{-6} M melatonin of AA-induced PRP aggregation and Tx _{B2} production was observed mainly in samples taken at 01.30 h. Assessed as a global effect, the inhibitory activity of melatonin on PRP Tx _{B2} showed a maximal effect at 01.30 h and a minimal effect at 09.30 h, at the time when plasma concentrations of melatonin were highest	125
Melatonin treatment ameliorated MS in obese patients	30 patients with MS who did not respond to 3-month lifestyle modification, and 33 healthy volunteers	Open-label trial	2 months	Melatonin (5 mg/day, 2 h before bedtime) for 2 months. Controls did not receive melatonin	Systolic and diastolic BP, levels of glucose, serum lipids, C-reactive protein, fibrinogen, activities of antioxidative enzymes	Melatonin treatment decreased significantly systolic BP, diastolic BP, low-density lipoprotein cholesterol and TBARS and augmented catalase activity	126
Melatonin treatment ameliorated MS in obese patients	39 MS patients	Double-blind, placebo-controlled, crossover, randomized trial	26 weeks	8.0 mg p.o. melatonin or placebo nightly for 10 weeks. After a 6-week washout, subjects received the other treatment for 10 more weeks	Waist circumference, triglycerides, high-density lipoprotein cholesterol, fasting glucose and BP at the beginning and end of both 10-week treatment periods	The mean 10-week change for most MS components favored melatonin over placebo (except fasting glucose). Freedom from MS tended to be more common following melatonin vs. placebo treatment	127
Melatonin treatment ameliorated the MS caused by second-generation antipsychotics in bipolar and schizophrenic patients	44 patients treated with second-generation antipsychotics (20 with bipolar disorder and 24 with schizo-phrenia)	Double-blind, randomized, placebo-controlled, parallel-group trial	8 weeks	Patients randomly received melatonin 5 mg p.o. at bedtime (n = 20) or placebo (n = 24)	Body weight, BP, lipid, glucose, body composition, and anthropometric measures	The melatonin group showed a decrease in diastolic BP and attenuated weight gain. The strong beneficial metabolic effects of melatonin in comparison to placebo on fat mass and diastolic BP were observed in the bipolar disorder and not in the schizophrenic group	128
Melatonin treatment ameliorated the MS caused by olanzapine in schizophrenic patients	48 patients with first-episode schizophrenia	Randomized double-blind placebo-controlled study	8 weeks	Patients randomly received melatonin 3 mg p.o. at bedtime or placebo	Anthropometric and metabolic parameters as well as psychiatric symptoms were assessed at baseline and weeks 4 and 8. Primary outcome measure was the change from baseline in weight at week 8	At week 8, melatonin was associated with significantly less weight gain, increase in waist circumference and triglyceride concentration than the placebo. Patients in the melatonin group experienced significantly more reduction in their psychiatric symptomatology than the placebo group	129
Melatonin treatment ameliorated the MS caused by olanzapine in adolescents with bipolar disorder	48 adolescent outpatients with bipolar mood disorder	Randomized placebo-controlled study	12 weeks	24 patients were allocated to olanzapine, lithium carbonate and 3 mg/day melatonin p.o., and 24 patients were allocated to olanzapine, lithium carbonate and placebo	Young Mania Rating Scale was performed at baseline. Before treatment initiation and at the 6th and 12th weeks after treatment, lipid profile, fasting blood sugar, systolic BP and diastolic BP were measured	Fasting glycemia and serum triglyceride demonstrated a trend for a greater increase in the placebo group compared to the melatonin group. Melatonin significantly inhibited the rise in total cholesterol levels. Mean systolic BP rose more slowly in the melatonin group compared to placebo	130
Melatonin treatment improved enzymatic profile in patients with nonalcoholic liver steatosis	42 patients with histological evidence (liver biopsy) of nonalcoholic liver steatohapatitis	Randomized placebo-controlled study	12 weeks	30 patients were allocated to 2 x 5 mg/day melatonin p.o., and 12 patients were allocated to placebo	BMI, plasma alanine aminotransferase, aspartate transpeptidase, alkaline phosphatase, cholesterol, triglycerides, glucose and melatonin	Aspartate aminotransferase and γ -glutamyl transpeptidase decreased significantly in melatonin-treated patients only. Plasma levels of triglycerides and glucose as well as BMI in controls and melatonin-treated patients were not significantly different from baseline	131

Table 2 (continued)

Finding	Subjects	Design	Study duration	Treatment	Measured	Results	Ref.
Melatonin treatment improved enzymatic profile in patients with nonalcoholic liver steatosis	42 patients with histological evidence (liver biopsy) of nonalcoholic steatohepatitis (follow-up of the previous study)	Randomized placebo-controlled study	24 weeks	30 patients were allocated to 2 x 5 mg/day melatonin p.o., and 12 patients were allocated to placebo	BMI, plasma alanine aminotransferase, aspartate aminotransferase, γ -glutamyl-transpeptidase, alkaline phosphatase, cholesterol, triglycerides, glucose and melatonin	Aspartate aminotransferase and γ -glutamyl transpeptidase decreased significantly in melatonin-treated patients only. Plasma levels of triglycerides and glucose as well as BMI in controls and melatonin-treated patients were not significantly different from baseline	132
Melatonin alone or in combination with metformin improved glycemic control in type 2 diabetic patients	46 type 2 diabetic patients	Placebo controlled, double-blind trial	90 days	Patients were allocated to 3 groups: (a) single daily oral doses of both 10 mg melatonin and 50 mg zinc acetate alone; (b) 10 mg melatonin and 50 mg zinc acetate in addition to the regularly used metformin; (c) placebo, all given at bedtime	Fasting plasma glucose, glycated hemoglobin (HbA1C) and serum C-peptide before starting the treatment and after 30 and 90 days of treatment	Daily administration of melatonin and zinc improved the impaired fasting and postprandial glycemic control and decreased the level of glycated hemoglobin. The addition of this treatment regimen in combination with metformin improved the tissue responses to this oral hypoglycemic agent	133
Melatonin treatment ameliorated oxidative stress and inflammatory parameters of obese women	44 obese women	Randomized double-blind, placebo-controlled trial	40 days	6 mg melatonin p.o. at bedtime	Serum TNF- α , IL-6, hsCRP, TAC, and MDA levels	In the melatonin group, mean serum TNF- α , IL-6, hsCRP and MDA levels decreased significantly, whilst in the placebo group the decrease in these values was not statistically significant. The mean TAC level increased in the melatonin group, whereas it decreased slightly in the placebo group. Melatonin decreased significantly TNF- α and IL-6 levels	134
Acute melatonin administration in healthy women impaired glucose tolerance	21 healthy young women	Randomized double-blind, placebo-controlled trial	4 nonconsecutive days	5 mg melatonin p.o	Glucose tolerance was assessed by oral glucose tolerance tests 15 min after melatonin or placebo administration on 4 occasions: in the morning (09.00 h) and evening (21.00 h)	Melatonin administration significantly impaired glucose tolerance. The effect of melatonin on insulin response depended on the time of day. In the morning, melatonin decreased glucose tolerance primarily by decreasing insulin release, while in the evening, by decreasing insulin sensitivity	135

AA = Arachidonic acid; aMT6s = 6-sulfatoxymelatonin; BP = blood pressure; hsCRP = human serum C-reactive protein; HR = heart rate; HRV = heart rate variability; MDA = malondialdehyde; PRP = platelet-rich plasma; RIA = radioimmunoassay; SNP = single nucleotide polymorphism; TAC = total antioxidant capacity; TBARS = thiobarbituric acid reactive substances; TxB2 = thromboxane B2.

in peri- and postmenopausal women [137]. Several mechanisms may explain the hypolipidemic effects of melatonin, such as reduced intestinal absorption of cholesterol [138] or inhibiting cholesterol biosynthesis [139].

Catecholamine-induced hypercoagulability in acute stress that contributes to the growth of thrombus after rupture of coronary plaque was prevented by the administration of melatonin [122]. This was probably mediated by the reported inhibitory effects of melatonin on platelet aggregation [123–125]. In light of these results, melatonin may have a protective effect in reducing atherothrombotic risk in MS.

Several studies support the beneficial role of melatonin in patients with MS. Melatonin treatment ameliorated MS in obese patients [126, 127] as well as in bipolar and schizophrenic patients after treatment with second generation antipsychotics [128–130]. Melatonin administration normalized MS in elderly hypertensive patients [140] and improved the enzymatic profile in patients with alcoholic liver steatosis [131, 132]. The combination of melatonin and zinc acetate, when used alone or in combination with metformin improved glycemic control in type 2 diabetic patients [133], and an inverse relationship between urinary 6-sulfatoxy melatonin excretion and insulin levels and insulin resistance was reported in healthy women in the Nurses' Health Study cohort [141]. However, a recent placebo-controlled single-blind study including 21 healthy women reported that melatonin (5 mg) decreased glucose tolerance [135]. Further studies are needed to clarify this controversy.

Overall, the results discussed above suggest that melatonin therapy may be beneficial for patients with MS. Undoubtedly, more studies are needed to evaluate an appropriate time/duration of treatment/dose relationship in the administration of melatonin in patients with MS.

As with many diseases, particularly those related to MS, hypertension, cardiovascular disease, obesity, diabetes, etc., the evidence supports the hypothesis that metabolic rhythm attenuation and/or disruption contribute to the etiology of the disease. Diabetes mellitus, a significant risk factor for developing heart disease and/or MS in humans, is associated with a phase change in the cardiac circadian clock [142]. Actually, metformin, a diabetes medication commonly used under Clinical Commissioning Group guidelines, increases the circadian amplitude of the metabolic sensor AMP kinase and modulates liver casein kinase 1 α (CK1 α) and muscle CK1 ϵ , two regulators of the respective circadian core oscillators, effects that influence the expression and temporal patterns of several clock components and key genes of energy metabolism [143].

Conclusions

Melatonin can provide an innovative strategy in MS by combining its effects on the circadian rhythm with its cytoprotective properties. Melatonin protects against several MS comorbidities, such as diabetes and concomitant oxyradical-mediated damage, inflammation, microvascular disease and atherothrombotic risk. At an early stage of the treatment of MS, a nondrug approach such as changing the lifestyle, low-fat diet and exercise is commonly recommended. Patients who are refractory to these changes are treated with antihypertensive drugs (antidiabetic, lipid-lowering drugs) that can have significant side effects.

Melatonin may thus be beneficial from the initial phases of MS treatment. It has a high safety profile and shows a reduced toxicity, thus differing from many pharmaceutical agents used in MS patients. Moreover, melatonin is usually remarkably well tolerated at very high doses [144]. As melatonin is a short-lived molecule that has a limited duration of action (half-life from 0.54 to 0.67 h, analogs with a high affinity for melatonin receptors and a longer duration of action have been synthesized to treat circadian disorders [145]. To what extent the new melatonergic agents approved by the US Food and Drug Administration or the European Medicines Agency (ramelteon, agomelatine, tasimelteon) share the protective activity of melatonin in MS remains to be defined. There is evidence that ramelteon given daily in drinking water (8 mg/kg) for 8 weeks to spontaneously hypertensive male Wistar-Kyoto rats significantly attenuated systolic blood pressure and body weight gain associated with age [146]. In addition, an investigational melatonergic agonist, piromelatine (NEU-P11), has been reported to be similarly effective or even superior to melatonin in improving some MS-associated parameters [52, 60, 147].

Given higher binding affinities, longer half-life and high relative potencies of the various melatonin agonists, studies using 2 or 3 mg/day of melatonin are probably inadequate to provide an adequate comparison with the effects of the natural compound. Doses that considerably exceed those usually applied have been found to be safe, e.g. in the treatment of ALS patients who received either 60 mg/day orally for up to 13 months [148] or 300 mg/day enterally for up to 2 years [144]. In a phase I dose escalation study in healthy volunteers to assess the tolerability and pharmacokinetics of 20-, 30-, 50-, and 100-mg oral doses of melatonin, no adverse effects after oral melatonin other than mild transient drowsiness, with no effects on sleeping patterns, were seen [149]. Therefore,

further clinical trials using dosages of melatonin in the range of 50–100 mg/day appear to be reasonable and are warranted. The priorities for populations, outcomes, and durations of these studies must be defined.

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References

- King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care* 1998;21:1414–1431.
- Smith CJ, Ryckman KK: Epigenetic and developmental influences on the risk of obesity, diabetes, and metabolic syndrome. *Diabetes Metab Syndr Obes* 2015;8:295–302.
- O'Neill S, O'Driscoll L: Metabolic syndrome: a closer look at the growing epidemic and its associated pathologies. *Obes Rev* 2015;16:1–12.
- Kesse-Guyot E, Julia C, Andreeva V, Fezeu L, Hercberg S, Galan P: Evidence of a cumulative effect of cardiometabolic disorders at midlife and subsequent cognitive function. *Age Ageing* 2015;44:648–654.
- Balistreri CR, Caruso C, Candore G: The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm* 2010;2010:802078.
- Makki K, Froguel P, Wolowczuk I: Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines. *ISRN Inflamm* 2013;2013:139239.
- Welty FK, Alforddagh A, Elajami TK: Targeting inflammation in metabolic syndrome. *Transl Res* 2016;167:257–280.
- Esser N, Paquot N, Scheen AJ: Inflammatory markers and cardiometabolic diseases. *Acta Clin Belg* 2015;70:193–199.
- Arpaci D, Gurkan TA, Yilmaz S, Ergenc H, Tamer A, Keser N, Gunduz H: The relationship between epicardial fat tissue thickness and visceral adipose tissue in lean patients with polycystic ovary syndrome. *J Ovarian Res* 2015;8:71.
- Sarvari AK, Vereb Z, Uray IP, Fesus L, Balajthy Z: Atypical antipsychotics induce both proinflammatory and adipogenic gene expression in human adipocytes in vitro. *Biochem Biophys Res Commun* 2014;450:1383–1389.
- Zhang Y, Zitsman JL, Hou J, Fennoy I, Guo K, Feinberg J, Leibel RL: Fat cell size and adipokine expression in relation to gender, depot, and metabolic risk factors in morbidly obese adolescents. *Obesity (Silver Spring)* 2014;22:691–697.
- Tchernof A, Despres JP: Pathophysiology of human visceral obesity: an update. *Physiol Rev* 2013;93:359–404.
- Franceschi C, Bonafe M, Valensin S, Olivieri F, De LM, Ottaviani E, De BG: Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann NY Acad Sci* 2000;908:244–254.
- Boren E, Gershwin ME: Inflamm-aging: autoimmunity, and the immune-risk phenotype. *Autoimmun Rev* 2004;3:401–406.
- Cevenini E, Monti D, Franceschi C: Inflamm-aging. *Curr Opin Clin Nutr Metab Care* 2013;16:14–20.
- De la Fuente M, Miquel J: An update of the oxidation-inflammation theory of aging: the involvement of the immune system in oxinflamm-aging. *Curr Pharm Des* 2009;15:3003–3026.
- Hardeland R: Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. *J Pineal Res* 2013;55:325–356.
- Caruso C, Candore G, Colonna RG, Lio D, Bonafe M, Valensin S, Franceschi C: HLA, aging, and longevity: a critical reappraisal. *Hum Immunol* 2000;61:942–949.
- Pawelec G, Derhovanessian E, Larbi A, Strindhall J, Wikby A: Cytomegalovirus and human immunosenescence. *Rev Med Virol* 2009;19:47–56.
- Pawelec G, Larbi A, Derhovanessian E: Senescence of the human immune system. *J Comp Pathol* 2010;142(suppl 1):S39–S44.
- Strindhall J, Nilsson BO, Lofgren S, Ernerudh J, Pawelec G, Johansson B, Wikby A: No immune risk profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. *Exp Gerontol* 2007;42:753–761.
- Candore G, Caruso C, Colonna-Romano G: Inflammation, genetic background and longevity. *Biogerontology* 2010;11:565–573.
- Franceschi C, Bonafe M: Centenarians as a model for healthy aging. *Biochem Soc Trans* 2003;31:457–461.
- DelaRosa O, Pawelec G, Peralbo E, Wikby A, Mariani E, Mocchegiani E, Tarazona R, Solana R: Immunological biomarkers of ageing in man: changes in both innate and adaptive immunity are associated with health and longevity. *Biogerontology* 2006;7:471–481.
- Ponnappan S, Ponnappan U: Aging and immune function: molecular mechanisms to interventions. *Antioxid Redox Signal* 2011;14:1551–1585.
- Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter RJ: Melatonin as a potent and inducible endogenous antioxidant: synthesis and metabolism. *Molecules* 2015;20:18886–18906.
- Hardeland R, Cardinali DP, Brown GM, Pandi-Perumal SR: Melatonin and brain inflammation. *Prog Neurobiol* 2015;127–128:46–63.
- Hardeland R: Melatonin in aging and disease – multiple consequences of reduced secretion, options and limits of treatment. *Aging Dis* 2012;3:194–225.
- Brugger P, Marktl W, Herold M: Impaired nocturnal secretion of melatonin in coronary heart disease. *Lancet* 1995;345:1408.
- Altun A, Yaprak M, Aktöz M, Vardar A, Betül UA, Ozbay G: Impaired nocturnal synthesis of melatonin in patients with cardiac syndrome X. *Neurosci Lett* 2002;327:143–145.
- Sakotnik A, Liebmann PM, Stoschitzky K, Lercher P, Schauenstein K, Klein W, Eber B: Decreased melatonin synthesis in patients with coronary artery disease. *Eur Heart J* 1999;20:1314–1317.
- Girotti L, Lago M, Ianovsky O, Carbajales J, Elizari MV, Brusco LI, Cardinali DP: Low urinary 6-sulphatoxymelatonin levels in patients with coronary artery disease. *J Pineal Res* 2000;29:138–142.
- Dominguez-Rodriguez A, Abreu-Gonzalez P, Garcia MJ, Sanchez J, Marrero F, de Armas-Trujillo D: Decreased nocturnal melatonin levels during acute myocardial infarction. *J Pineal Res* 2002;33:248–252.
- Yaprak M, Altun A, Vardar A, Aktöz M, Ciftci S, Ozbay G: Decreased nocturnal synthesis of melatonin in patients with coronary artery disease. *Int J Cardiol* 2003;89:103–107.
- O'Brien IA, Lewin IG, O'Hare JP, Arendt J, Corral RJ: Abnormal circadian rhythm of melatonin in diabetic autonomic neuropathy. *Clin Endocrinol (Oxf)* 1986;24:359–364.
- Tutuncu NB, Batur MK, Yildirim A, Tutuncu T, Deger A, Koray Z, Erbas B, Kabakci G, Aksoyek S, Erbas T: Melatonin levels decrease in type 2 diabetic patients with cardiac autonomic neuropathy. *J Pineal Res* 2005;39:43–49.
- Contreras-Alcantara S, Baba K, Tosini G: Removal of melatonin receptor type 1 induces insulin resistance in the mouse. *Obesity (Silver Spring)* 2010;18:1861–1863.
- Zanquetta MM, Seraphim PM, Sumida DH, Cipolla-Neto J, Machado UF: Calorie restriction reduces pinealectomy-induced insulin resistance by improving GLUT4 gene expression and its translocation to the plasma membrane. *J Pineal Res* 2003;35:141–148.
- Nogueira TC, Lellis-Santos C, Jesus DS, Tameda M, Rodrigues SC, Amaral FG, Lopes AM, Cipolla-Neto J, Bordin S, Anhe GF: Absence of melatonin induces night-time hepatic insulin resistance and increased gluconeogenesis due to stimulation of nocturnal unfolded protein response. *Endocrinology* 2011;152:1253–1263.

- 40 Cuesta S, Kireev R, Garcia C, Rancan L, Vara E, Tresguerres JA: Melatonin can improve insulin resistance and aging-induced pancreas alterations in senescence-accelerated prone male mice (SAMP8). *Age (Dordr)* 2013;35:659–671.
- 41 She M, Hou H, Wang Z, Zhang C, Laudon M, Yin W: Melatonin rescues 3T3-L1 adipocytes from FFA-induced insulin resistance by inhibiting phosphorylation of IRS-1 on Ser307. *Biochimie* 2014;103:126–130.
- 42 Teodoro BG, Baraldi FG, Sampaio IH, Bomfim LH, Queiroz AL, Passos MA, Carneiro EM, Alberici LC, Gomis R, Amaral FG, Cipolla-Neto J, Araujo MB, Lima T, Uyemura SA, Silveira LR, Vieira E: Melatonin prevents mitochondrial dysfunction and insulin resistance in rat skeletal muscle. *J Pineal Res* 2014; 57:155–167.
- 43 Quan X, Wang J, Liang C, Zheng H, Zhang L: Melatonin inhibits tunicamycin-induced endoplasmic reticulum stress and insulin resistance in skeletal muscle cells. *Biochem Biophys Res Commun* 2015;463:1102–1107.
- 44 Prunet-Marcassus B, Desbazeille M, Bros A, Louche K, Delagrangre P, Renard P, Casteilla L, Penicaud L: Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. *Endocrinology* 2003;144: 5347–5352.
- 45 Puchalski SS, Green JN, Rasmussen DD: Melatonin effect on rat body weight regulation in response to high-fat diet at middle age. *Endocrine* 2003;21:163–167.
- 46 Sartori C, Dessen P, Mathieu C, Monney A, Bloch J, Nicod P, Scherrer U, Duplain H: Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology* 2009;150:5311–5317.
- 47 Ladizesky MG, Boggio V, Albornoz LE, Castillon PO, Mautalen C, Cardinali DP: Melatonin increases oestradiol-induced bone formation in ovariectomized rats. *J Pineal Res* 2003;34:143–151.
- 48 Sanchez-Mateos S, Alonso-Gonzalez C, Gonzalez A, Martinez-Campa CM, Mediavilla MD, Cos S, Sanchez-Barcelo EJ: Melatonin and estradiol effects on food intake, body weight, and leptin in ovariectomized rats. *Maturnitas* 2007;58:91–101.
- 49 Ciortea R, Costin N, Braicu I, Haragas D, Hudacsko A, Bondor C, Miha D, Miha CM: Effect of melatonin on intra-abdominal fat in correlation with endometrial proliferation in ovariectomized rats. *Anticancer Res* 2011;31: 2637–2643.
- 50 Raskind MA, Burke BL, Crites NJ, Tapp AM, Rasmussen DD: Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. *Neuropsychopharmacology* 2007;32: 284–288.
- 51 De PN, Martinez-Alvarez RM, Delgado MJ: Melatonin reduces body weight in goldfish (*Carassius auratus*): effects on metabolic resources and some feeding regulators. *J Pineal Res* 2008;45:32–39.
- 52 She M, Deng X, Guo Z, Laudon M, Hu Z, Liao D, Hu X, Luo Y, Shen Q, Su Z, Yin W: NEUP11, a novel melatonin agonist, inhibits weight gain and improves insulin sensitivity in high-fat/high-sucrose-fed rats. *Pharmacol Res* 2009;59:248–253.
- 53 Rios-Lugo MJ, Cano P, Jimenez-Ortega V, Fernandez-Mateos MP, Scacchi PA, Cardinali DP, Esquifino AI: Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. *J Pineal Res* 2010;49:342–348.
- 54 Nduhirabandi F, du Toit EF, Blackhurst D, Marais D, Lochner A: Chronic melatonin consumption prevents obesity-related metabolic abnormalities and protects the heart against myocardial ischemia and reperfusion injury in a prediabetic model of diet-induced obesity. *J Pineal Res* 2011;50:171–182.
- 55 Agil A, Navarro-Alarcon M, Ruiz R, Abuhamad S, El-Mir MY, Vazquez GF: Beneficial effects of melatonin on obesity and lipid profile in young Zucker diabetic fatty rats. *J Pineal Res* 2011;50:207–212.
- 56 Kitagawa A, Ohta Y, Ohashi K: Melatonin improves metabolic syndrome induced by high fructose intake in rats. *J Pineal Res* 2012;52: 403–413.
- 57 Cardinali DP, Bernasconi PA, Reynoso R, Toso CF, Scacchi P: Melatonin may curtail the metabolic syndrome: studies on initial and fully established fructose-induced metabolic syndrome in rats. *Int J Mol Sci* 2013;14:2502–2514.
- 58 Bernasconi PA, Cardoso NP, Reynoso R, Scacchi P, Cardinali DP: Melatonin and diet-induced metabolic syndrome in rats: impact on the hypothalamic-testicular axis. *Horm Mol Biol Clin Invest* 2013;16:101–112.
- 59 Demirtas CY, Pasaoglu OT, Bircan FS, Kantar S, Turkozkan N: The investigation of melatonin effect on liver antioxidant and oxidant levels in fructose-mediated metabolic syndrome model. *Eur Rev Med Pharmacol Sci* 2015;19:1915–1921.
- 60 Huang L, Zhang C, Hou Y, Laudon M, She M, Yang S, Ding L, Wang H, Wang Z, He P, Yin W: Blood pressure reducing effects of piromelatine and melatonin in spontaneously hypertensive rats. *Eur Rev Med Pharmacol Sci* 2013;17:2449–2456.
- 61 Vinogradova I, Anisimov V: Melatonin prevents the development of the metabolic syndrome in male rats exposed to different light/dark regimens. *Biogerontology* 2013;14:401–409.
- 62 Hatzis G, Ziakas P, Kavantzias N, Triantafyllou A, Sigalas P, Andreadou I, Ioannidis K, Chatzis S, Filis K, Papalampros A, Sigala F: Melatonin attenuates high fat diet-induced fatty liver disease in rats. *World J Hepatol* 2013;5:160–169.
- 63 Diez ER, Renna NF, Prado NJ, Lembo C, Ponce Zumino AZ, Vazquez-Prieto M, Mitello RM: Melatonin, given at the time of reperfusion, prevents ventricular arrhythmias in isolated hearts from fructose-fed rats and spontaneously hypertensive rats. *J Pineal Res* 2013;55:166–173.
- 64 Agil A, Reiter RJ, Jimenez-Aranda A, Iban-Arias R, Navarro-Alarcon M, Marchal JA, Adem A, Fernandez-Vazquez G: Melatonin ameliorates low-grade inflammation and oxidative stress in young Zucker diabetic fatty rats. *J Pineal Res* 2013;54:381–388.
- 65 Pai SA, Majumdar AS: Protective effects of melatonin against metabolic and reproductive disturbances in polycystic ovary syndrome in rats. *J Pharm Pharmacol* 2014;66:1710–1721.
- 66 Cano BP, Pagano ES, Jimenez-Ortega V, Fernandez-Mateos P, Esquifino AI, Cardinali DP: Melatonin normalizes clinical and biochemical parameters of mild inflammation in diet-induced metabolic syndrome in rats. *J Pineal Res* 2014;57:280–290.
- 67 Rios-Lugo MJ, Jimenez-Ortega V, Cano-Barquilla P, Mateos PF, Spinedi EJ, Cardinali DP, Esquifino AI: Melatonin counteracts changes in hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats. *Horm Mol Biol Clin Invest* 2015;21: 175–183.
- 68 Favero G, Stacchiotti A, Castrezzati S, Bonomini F, Albanese M, Rezzani R, Rodella LF: Melatonin reduces obesity and restores adipokine patterns and metabolism in obese (ob/ob) mice. *Nutr Res* 2015;35:891–900.
- 69 Du Y, Wei T: Inputs and outputs of insulin receptor. *Protein Cell* 2014;5:203–213.
- 70 Verdile G, Keane KN, Cruzat VF, Medic S, Sabale M, Rowles J, Wijesekara N, Martins RN, Fraser PE, Newsholme P: Inflammation and oxidative stress: the molecular connectivity between insulin resistance, obesity, and Alzheimer's Disease. *Mediators Inflamm* 2015;2015:105828.
- 71 Hardeland R, Cardinali DP, Srinivasan V, Spence DW, Brown GM, Pandi-Perumal SR: Melatonin – a pleiotropic, orchestrating regulator molecule. *Prog Neurobiol* 2011;93:350–384.
- 72 Escames G, Lopez A, Garcia JA, Garcia L, Acuna-Castroviejo D, Garcia JJ, Lopez LC: The role of mitochondria in brain aging and the effects of melatonin. *Curr Neuropharmacol* 2010;8:182–193.
- 73 Cardinali DP, Pagano ES, Scacchi Bernasconi PA, Reynoso R, Scacchi P: Melatonin and mitochondrial dysfunction in the central nervous system. *Horm Behav* 2013;63:322–330.
- 74 Agil A, El-Hammadi M, Jimenez-Aranda A, Tassi M, Abdo W, Fernandez-Vazquez G, Reiter RJ: Melatonin reduces hepatic mitochondrial dysfunction in diabetic obese rats. *J Pineal Res* 2015;59:70–79.
- 75 Hardeland R: Melatonin and its metabolites as anti-nitrosating and anti-nitrating agents. *J Exp Integr Med* 2011;1:67–81.
- 76 Wu UI, Mai FD, Sheu JN, Chen LY, Liu YT, Huang HC, Chang HM: Melatonin inhibits microglial activation, reduces pro-inflammatory cytokine levels, and rescues hippocampal neurons of adult rats with acute *Klebsiella pneumoniae* meningitis. *J Pineal Res* 2011;50: 159–170.

- 77 Ding K, Wang H, Xu J, Lu X, Zhang L, Zhu L: Melatonin reduced microglial activation and alleviated neuroinflammation induced neuron degeneration in experimental traumatic brain injury: possible involvement of mTOR pathway. *Neurochem Int* 2014;76:23–31.
- 78 Hardeland R: Neuroprotection by radical avoidance: search for suitable agents. *Molecules* 2009;14:5054–5102.
- 79 Carrillo-Vico A, Lardone PJ, Alvarez-Sanchez N, Rodriguez-Rodriguez A, Guerrero JM: Melatonin: buffering the immune system. *Int J Mol Sci* 2013;14:8638–8683.
- 80 Cardinali DP, Garcia AP, Cano P, Esquifino AI: Melatonin role in experimental arthritis. *Curr Drug Targets Immune Endocr Metabol Disord* 2004;4:1–10.
- 81 Maestroni GJ, Cardinali DP, Esquifino AI, Pandi-Perumal SR: Does melatonin play a disease-promoting role in rheumatoid arthritis? *J Neuroimmunol* 2005;158:106–111.
- 82 Kireev RA, Tresguerres AC, Garcia C, Ariznavarreta C, Vara E, Tresguerres JA: Melatonin is able to prevent the liver of old castrated female rats from oxidative and pro-inflammatory damage. *J Pineal Res* 2008;45:394–402.
- 83 Kireev RA, Vara E, Vina J, Tresguerres JA: Melatonin and oestrogen treatments were able to improve neuroinflammation and apoptotic processes in dentate gyrus of old ovariectomized female rats. *Age (Dordr)* 2014;36:9707.
- 84 Cuesta S, Kireev R, Forman K, Garcia C, Escames G, Ariznavarreta C, Vara E, Tresguerres JA: Melatonin improves inflammation processes in liver of senescence-accelerated prone male mice (SAMP8). *Exp Gerontol* 2010;45:950–956.
- 85 Cuesta S, Kireev R, Garcia C, Forman K, Escames G, Vara E, Tresguerres JA: Beneficial effect of melatonin treatment on inflammation, apoptosis and oxidative stress on pancreas of a senescence accelerated mice model. *Mech Ageing Dev* 2011;132:573–582.
- 86 Forman K, Vara E, Garcia C, Kireev R, Cuesta S, Escames G, Tresguerres JA: Effect of a combined treatment with growth hormone and melatonin in the cardiological aging on male SAMP8 mice. *J Gerontol A Biol Sci Med Sci* 2011;66:823–834.
- 87 Hardeland R: Melatonin: signaling mechanisms of a pleiotropic agent. *Biofactors* 2009;35:183–192.
- 88 Hardeland R, Madrid JA, Tan DX, Reiter RJ: Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J Pineal Res* 2012;52:139–166.
- 89 Sahar S, Sassone-Corsi P: The epigenetic language of circadian clocks. *Handb Exp Pharmacol* 2013;29–44.
- 90 Hardeland R: Melatonin and circadian oscillators in aging – a dynamic approach to the multiply connected players. *Interdiscip Top Gerontol* 2015;40:128–140.
- 91 Muhlbauer E, Wolgast S, Finckh U, Peschke D, Peschke E: Indication of circadian oscillations in the rat pancreas. *FEBS Lett* 2004;564:91–96.
- 92 Hardeland R, Madrid JA, Tan DX, Reiter RJ: Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling. *J Pineal Res* 2012;52:139–166.
- 93 Boivin DB, James FO, Wu A, Cho-Park PF, Xiong H, Sun ZS: Circadian clock genes oscillate in human peripheral blood mononuclear cells. *Blood* 2003;102:4143–4145.
- 94 Bollinger T, Leutz A, Leliavski A, Skrum L, Kovac J, Bonacina L, Benedict C, Lange T, Westermann J, Oster H, Solbach W: Circadian clocks in mouse and human CD4+ T cells. *PLoS One* 2011;6:e29801.
- 95 Jung KH, Hong SW, Zheng HM, Lee DH, Hong SS: Melatonin downregulates nuclear erythroid 2-related factor 2 and nuclear factor-kappaB during prevention of oxidative liver injury in a dimethylnitrosamine model. *J Pineal Res* 2009;47:173–183.
- 96 Jung KH, Hong SW, Zheng HM, Lee HS, Lee H, Lee DH, Lee SY, Hong SS: Melatonin ameliorates cerulein-induced pancreatitis by the modulation of nuclear erythroid 2-related factor 2 and nuclear factor-kappaB in rats. *J Pineal Res* 2010;48:239–250.
- 97 Korkmaz A, Rosales-Corral S, Reiter RJ: Gene regulation by melatonin linked to epigenetic phenomena. *Gene* 2012;503:1–11.
- 98 Bellet MM, Orozco-Solis R, Sahar S, Eckel-Mahan K, Sassone-Corsi P: The time of metabolism: NAD+, SIRT1, and the circadian clock. *Cold Spring Harb Symp Quant Biol* 2011;76:31–38.
- 99 Hardeland R: Melatonin, noncoding RNAs, messenger RNA stability and epigenetics – evidence, hints, gaps and perspectives. *Int J Mol Sci* 2014;15:18221–18252.
- 100 Pan M, Song YL, Xu JM, Gan HZ: Melatonin ameliorates nonalcoholic fatty liver induced by high-fat diet in rats. *J Pineal Res* 2006;41:79–84.
- 101 Stumpf I, Bazwinsky I, Peschke E: Modulation of the cGMP signaling pathway by melatonin in pancreatic beta-cells. *J Pineal Res* 2009;46:140–147.
- 102 Kanter M, Uysal H, Karaca T, Sagmanligil HO: Depression of glucose levels and partial restoration of pancreatic beta-cell damage by melatonin in streptozotocin-induced diabetic rats. *Arch Toxicol* 2006;80:362–369.
- 103 Nishida S, Sato R, Murai I, Nakagawa S: Effect of pinealectomy on plasma levels of insulin and leptin and on hepatic lipids in type 2 diabetic rats. *J Pineal Res* 2003;35:251–256.
- 104 Nishida S, Segawa T, Murai I, Nakagawa S: Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of Delta-5 desaturase activity. *J Pineal Res* 2002;32:26–33.
- 105 Mazepa RC, Cuevas MJ, Collado PS, Gonzalez-Gallego J: Melatonin increases muscle and liver glycogen content in nonexercised and exercised rats. *Life Sci* 2000;66:153–160.
- 106 Shieh JM, Wu HT, Cheng KC, Cheng JT: Melatonin ameliorates high fat diet-induced diabetes and stimulates glycogen synthesis via a PKCzeta-Akt-GSK3beta pathway in hepatic cells. *J Pineal Res* 2009;47:339–344.
- 107 Bartness TJ, Demas GE, Song CK: Seasonal changes in adiposity: the roles of the photoperiod, melatonin and other hormones, and sympathetic nervous system. *Exp Biol Med (Maywood)* 2002;227:363–376.
- 108 Tan DX, Manchester LC, Fuentes-Broto L, Paredes SD, Reiter RJ: Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. *Obes Rev* 2011;12:167–188.
- 109 Peschke E, Stumpf I, Bazwinsky I, Litvak L, Dralle H, Muhlbauer E: Melatonin and type 2 diabetes – a possible link? *J Pineal Res* 2007;42:350–358.
- 110 Prokopenko I, Langenberg C, Florez JC, Saxena R, et al: Variants in MTNR1B influence fasting glucose levels. *Nat Genet* 2009;41:77–81.
- 111 Huber M, Treszl A, Reibis R, Teichmann C, Zergibel I, Bolbrinker J, Scholze J, Wegscheider K, Voller H, Kreutz R: Genetics of melatonin receptor type 2 is associated with left ventricular function in hypertensive patients treated according to guidelines. *Eur J Intern Med* 2013;24:650–655.
- 112 Zheng C, Dalla MC, 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.
- 113 Song X, Sun X, Ma G, Sun Y, Shi Y, Du Y, Chen ZJ: Family association study between melatonin receptor gene polymorphisms and polycystic ovary syndrome in Han Chinese. *Eur J Obstet Gynecol Reprod Biol* 2015;195:108–112.
- 114 Obayashi K, Saeki K, Iwamoto J, Okamoto N, Tomioka K, Nezu S, Ikada Y, Kurumatani N: Nocturnal urinary melatonin excretion is associated with non-dipper pattern in elderly hypertensives. *Hypertens Res* 2013;36:736–740.
- 115 Cavallo A, Daniels SR, Dolan LM, Khoury JC, Bean JA: Blood pressure response to melatonin in type 1 diabetes. *Pediatr Diabetes* 2004;5:26–31.
- 116 Cavallo A, Daniels SR, Dolan LM, Bean JA, Khoury JC: Blood pressure-lowering effect of melatonin in type 1 diabetes. *J Pineal Res* 2004;36:262–266.
- 117 Scheer FA, Van Montfrans GA, Van Someren EJ, Mairuhu G, Buijs RM: Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. *Hypertension* 2004;43:192–197.

- 118 Cagnacci A, Cannoletta M, Renzi A, Baldassari F, Arangino S, Volpe A: Prolonged melatonin administration decreases nocturnal blood pressure in women. *Am J Hypertens* 2005;18:1614–1618.
- 119 Grossman E, Laudon M, Yalcin R, Zengil H, Peleg E, Sharabi Y, Kamari Y, Shen-Orr Z, Zisapel N: Melatonin reduces night blood pressure in patients with nocturnal hypertension. *Am J Med* 2006;119:898–902.
- 120 Mozdzan M, Mozdzan M, Chalubinski M, Wojdan K, Broncel M: The effect of melatonin on circadian blood pressure in patients with type 2 diabetes and essential hypertension. *Arch Med Sci* 2014;10:669–675.
- 121 Gubin DG, Gubin GD, Gapon LI, Weinert D: Daily melatonin administration attenuates age-dependent disturbances of cardiovascular rhythms. *Curr Aging Sci* 2016;9:5–13.
- 122 Wirtz PH, Bartschi C, Spillmann M, Ehlert U, von Kanel R: Effect of oral melatonin on the procoagulant response to acute psychosocial stress in healthy men: a randomized placebo-controlled study. *J Pineal Res* 2008;44:358–365.
- 123 Del Zar MM, Martinuzzo M, Falcon C, Cardinali DP, Carreras LO, Vacas MI: Inhibition of human platelet aggregation and thromboxane-B2 production by melatonin: evidence for a diurnal variation. *J Clin Endocrinol Metab* 1990;70:246–251.
- 124 Del Zar MM, Martinuzzo M, Cardinali DP, Carreras LO, Vacas MI: Diurnal variation in melatonin effect on adenosine triphosphate and serotonin release by human platelets. *Acta Endocrinol (Copenh)* 1990;123:453–458.
- 125 Vacas MI, Del Zar MM, Martinuzzo M, Falcon C, Carreras LO, Cardinali DP: Inhibition of human platelet aggregation and thromboxane B2 production by melatonin. Correlation with plasma melatonin levels. *J Pineal Res* 1991;11:135–139.
- 126 Kozirog M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M: Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. *J Pineal Res* 2011;50:261–266.
- 127 Goyal A, Terry PD, Superak HM, Nell-Dybdahl CL, Chowdhury R, Phillips LS, Kutner MH: Melatonin supplementation to treat the metabolic syndrome: a randomized controlled trial. *Diabetol Metab Syndr* 2014;6:124.
- 128 Romo-Nava F, Alvarez-Icaza GD, Fresan-Orellana A, Saracco AR, 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;16:410–421.
- 129 Modabbernia A, Heidari P, Soleimani R, Sobhani A, Roshan ZA, Taslimi S, Ashrafi M, Modabbernia MJ: Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. *J Psychiatr Res* 2014;53:133–140.
- 130 Mostafavi A, Solhi M, Mohammadi MR, Hamedi M, Keshavarzi M, Akhondzadeh S: Melatonin decreases olanzapine induced metabolic side-effects in adolescents with bipolar disorder: a randomized double-blind placebo-controlled trial. *Acta Med Iran* 2014;52:734–739.
- 131 Gonciarz M, Gonciarz Z, Bielanski W, Mularczyk A, Konturek PC, Brzozowski T, Konturek SJ: The pilot study of 3-month course of melatonin treatment of patients with nonalcoholic steatohepatitis: effect on plasma levels of liver enzymes, lipids and melatonin. *J Physiol Pharmacol* 2010;61:705–710.
- 132 Gonciarz M, Gonciarz Z, Bielanski W, Mularczyk A, Konturek PC, Brzozowski T, Konturek SJ: The effects of long-term melatonin treatment on plasma liver enzymes levels and plasma concentrations of lipids and melatonin in patients with nonalcoholic steatohepatitis: a pilot study. *J Physiol Pharmacol* 2012;63:35–40.
- 133 Hussain SA, Khadim HM, Khalaf BH, Ismail SH, Hussein KI, Sahib AS: Effects of melatonin and zinc on glycemic control in type 2 diabetic patients poorly controlled with metformin. *Saudi Med J* 2006;27:1483–1488.
- 134 Mesri AN, Mahdavi R, Roshanravan N, Lotfi YN, Ostadrahimi AR, Faramarzi E: A double-blind, placebo-controlled trial related to the effects of melatonin on oxidative stress and inflammatory parameters of obese women. *Horm Metab Res* 2015;47:504–508.
- 135 Rubio-Sastre P, Scheer FA, Gomez-Abellan P, Madrid JA, Garaulet M: Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. *Sleep* 2014;37:1715–1719.
- 136 Grossman E, Laudon M, Zisapel N: Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. *Vasc Health Risk Manag* 2011;7:577–584.
- 137 Tamura H, Nakamura Y, Narimatsu A, Yamagata Y, Takasaki A, Reiter RJ, Sugino N: Melatonin treatment in peri- and postmenopausal women elevates serum high-density lipoprotein cholesterol levels without influencing total cholesterol levels. *J Pineal Res* 2008;45:101–105.
- 138 Hussain SA: Effect of melatonin on cholesterol absorption in rats. *J Pineal Res* 2007;42:267–271.
- 139 Esquifino AI, Agrasal C, Velazquez E, Villanua M, Cardinali DP: Effect of melatonin on serum cholesterol and phospholipid levels, and on prolactin, thyroid-stimulating hormone and thyroid hormone levels, in hyperprolactinemic rats. *Life Sci* 1997;11:1051–1058.
- 140 Shatilov VB, Bondarenko EV, Antoniuk-Shcheglova IA: Pineal gland melatonin-producing function in elderly patients with hypertensive disease: age peculiarities (in Russian). *Adv Gerontol* 2010;23:539–542.
- 141 McMullan CJ, Curhan GC, Schernhammer ES, Forman JP: Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. *Am J Epidemiol* 2013;178:231–238.
- 142 Chatham JC, Young ME: Regulation of myocardial metabolism by the cardiomyocyte circadian clock. *J Mol Cell Cardiol* 2013;55:139–146.
- 143 Barnea M, Haviv L, Gutman R, Chapnik N, Madar Z, Froy O: Metformin affects the circadian clock and metabolic rhythms in a tissue-specific manner. *Biochim Biophys Acta* 2012;1822:1796–1806.
- 144 Weishaupt JH, Bartels C, Polking E, Dietrich J, Rohde G, Poggeler B, Mertens N, Sperling S, Bohn M, Huther G, Schneider A, Bach A, Siren AL, Hardeland R, Bahr M, Nave KA, Ehrenreich H: Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. *J Pineal Res* 2006;41:313–323.
- 145 Cardinali DP, Srinivasan V, Brzezinski A, Brown GM: Melatonin and its analogs in insomnia and depression. *J Pineal Res* 2012;52:365–375.
- 146 Oxenkrug GF, Summergrad P: Ramelteon attenuates age-associated hypertension and weight gain in spontaneously hypertensive rats. *Ann NY Acad Sci* 2010;1199:114–120.
- 147 She M, Hu X, Su Z, Zhang C, Yang S, Ding L, Laudon M, Yin W: Piromelatine, a novel melatonin receptor agonist, stabilizes metabolic profiles and ameliorates insulin resistance in chronic sleep restricted rats. *Eur J Pharmacol* 2014;727:60–65.
- 148 Jacob S, Poggeler B, Weishaupt JH, Siren AL, Hardeland R, Bahr M, Ehrenreich H: Melatonin as a candidate compound for neuroprotection in amyotrophic lateral sclerosis (ALS): high tolerability of daily oral melatonin administration in ALS patients. *J Pineal Res* 2002;33:186–187.
- 149 Galley HF, Lowes DA, Allen L, Cameron G, Aucott LS, Webster NR: Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. *J Pineal Res* 2014;56:427–438.

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