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MULTI-AUTHOR REVIEW

Melatonin, mitochondria, and the metabolic syndrome

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Abstract A number of risk factors for cardiovascular disease including hyperinsulinemia, glucose intolerance, dyslipidemia, obesity, and elevated blood pressure are collectively known as metabolic syndrome (MS). Since mitochondrial activity is modulated by the availability of energy in cells, the disruption of key regulators of metabolism in MS not only affects the activity of mitochondria but also their dynamics and turnover. Therefore, a link of MS with mitochondrial dysfunction has been suspected since long. As a chronobiotic/cytoprotective agent, melatonin has a special place in prevention and treatment of MS. Melatonin levels are reduced in diseases associated with insulin resistance like MS. Melatonin improves sleep efficiency and has antioxidant and anti-inflammatory properties, partly for its role as a metabolic regulator and mitochondrial protector. We discuss in the present review the several cytoprotective melatonin actions that attenuate inflammatory responses in MS. The clinical data that support the potential therapeutical value of melatonin in human MS are reviewed.

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

Abbreviations

AMPK	Adenosine monophosphate kinase
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
GSH	Glutathione
HbA1C	Glycated hemoglobin
IRS-1	Insulin receptor substrate 1
IL	Interleukin
mTOR	Mammalian target of rapamycin
MS	Metabolic syndrome
mPTP	Mitochondrial permeability transition pore
NAD+	Nicotinamide adenine dinucleotide+
NO	Nitric oxide
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SNPs	Single-nucleotide polymorphisms
TNF	Tumor necrosis factor

Introduction

A number of risk factors for cardiovascular disease including hyperinsulinemia, glucose intolerance, dyslipidemia, obesity, and elevated blood pressure (BP) are collectively known as metabolic syndrome (MS). MS prevalence ranges from 15 to 30% depending on the world region considered [1, 2]. A 1.5- to 2.5-fold increase in cardiovascular mortality occurs when MS is present, representing one of the major public health problems nowadays.

The link of MS and mitochondrial dysfunction has been suspected since long. Mitochondrial activity is modulated by the availability of energy in cells and the disruption of key regulators of metabolism not only affects the activity of mitochondria but also their dynamics and turnover [3, 4]. Mitochondrial dysfunction is associated with the functional decline found in tissues and organs during many age-related diseases such as MS and diabetes. Recently, a study carried out in nondiabetic participants from the Baltimore Longitudinal Study of Aging

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has associated impaired mitochondrial capacity with greater insulin resistance [5].

MS is preventable. The excessive fat accumulation, either in white adipose tissue or other organs, is the consequence of hypertrophy and hyperplasia of white adipocytes in a context of positive energy balance. Without question, poor diet, lack of exercise, and chronic insulin resistance are major contributing factors to excessive fat accumulation [6, 7]. The abnormal nutritional balance is controlled mainly at the hypothalamic level by a complex circuitry of orexigenic and anorexigenic signals and by an endogenous clock that sets a circadian rhythm of appetite–satiety, a function highly affected by modern life habits.

In the last decade, there has been a considerable increase in our understanding of the cellular and molecular factors that contribute to MS development. One basic function that appears to be heavily influenced by (and influences) obesity and metabolic disease is the internal timing system [8–10]. The correlation between increased occurrence of obesity and the ubiquity of modern social habits, such as light at night, unusual meal timing, irregular sleep/wake schedules, and traveling between different time zones, all encompassed by a "24/7" lifestyle, strongly suggests that impairment of sleep and the circadian system is involved in the etiology of MS. Several clinical surveys have shown increased prevalence of MS in night-shift workers, indicating that artificial lighting may contribute to the increased prevalence of metabolic disorders [11–14]. Thus, both animal and human data have clearly proved that circadian and sleep disruption leads to insulin resistance and MS. In a study performed with 593 type 2 diabetes mellitus patients, sleep debt was associated with long-term metabolic disruption, which may promote the progression of the disease. For every 30 min of weekday sleep debt, the risk of obesity and insulin resistance at 12 months increased by 18 and 41%, respectively [15]. Collectively, these findings indicate the need for improving sleep quality to prevent the development of obesity and insulin resistance as well as its progression to diabetes.

As a chronobiotic/cytoprotective agent, melatonin has a special place in prevention and treatment of MS [16, 17]. Melatonin improves sleep efficiency and has antioxidant and anti-inflammatory properties, partly for its role as a metabolic regulator and mitochondrial protector [18–20]. This review summarizes what is known about a putative therapeutic role of melatonin concerning MS prevention and treatment. Medical literature was identified by searching databases including (MEDLINE and EMBASE), bibliographies from the published literature and clinical trial registries/databases. Searches were last updated on April 30, 2017.

Mitochondria, inflammation, and the metabolic syndrome

Low degree inflammation in white adipose tissue leads to impaired glucose tolerance, insulin resistance, and diabetes [21, 22] (Fig. 1). Tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, leptin, and resistin give rise to a vicious circle leading to fat deposition. Occurrence of inflammation in obesity is also supported by the increase in C-reactive protein and other inflammatory biomarkers [23, 24].

Early MS is characterized by the increased systemic markers of lipid oxidation, such as oxidized low-density lipoproteins and isoprostanes, which contribute to the development of insulin resistance [3–5]. In the mitochondria, lipid peroxidation particularly affects cardiolipin, a phospholipid located at the level of inner mitochondrial membrane, which is required for several mitochondrial bioenergetic processes as well as in mitochondrial-dependent steps of apoptosis (e.g., it prevents the opening of the mitochondrial permeability transition pore (mPTP). Alterations in cardiolipin structure, content, and acyl chain composition have been associated with mitochondrial dysfunction in various tissues under a variety of pathophysiological conditions [25].

Among mitochondrial regulators, the mammalian target of rapamycin (mTOR), which is activated by high calorie intake or high levels of amino acids, plays an important role [26]. The signaling pathway triggered by mTOR competes against other regulators of the cell metabolism such as adenosine monophosphate kinase (AMPK) and sirtuins, and nicotinamide adenine dinucleotide^{+} (NAD^{+})-dependent deacetylases that induce more efficient energy consumption in situations of low intake, starvation, or calorie restriction [27].

In obesity, promotion of fat mass is given by proinflammatory cytokines acting via paracrine mechanisms [28–30]. In obese patients, proinflammatory molecules derived from adipose tissue diminish after weight loss [31]. Thus, source as well as a target for proinflammatory cytokines are given by fat cells. When white adipose tissue mass increases by adipocyte hypertrophy, the large-size adipocytes develop a secretory dysfunction characterized by overproduction (synthesis and release) of adipocytokines that decrease tissue sensitivity to insulin, promote oxidative stress, and display proinflammatory effects (leptin, resistin, TNF-α, plasminogen activator inhibitor-1, IL-1, and IL-6). In addition, lower amounts of adiponectin (an insulin-sensitizing adipokine) are released by adipocytes (Fig. 1). Consequently, obesity is the result of a multifactorial combination of genetic background, metabolic, endocrine, inflammatory, and circadian dysfunctions, whose long-term maintenance is favored by behavioral disorders [32].

Even in the absence of physiological stress or acute infection, levels of inflammatory mediators increase with age.

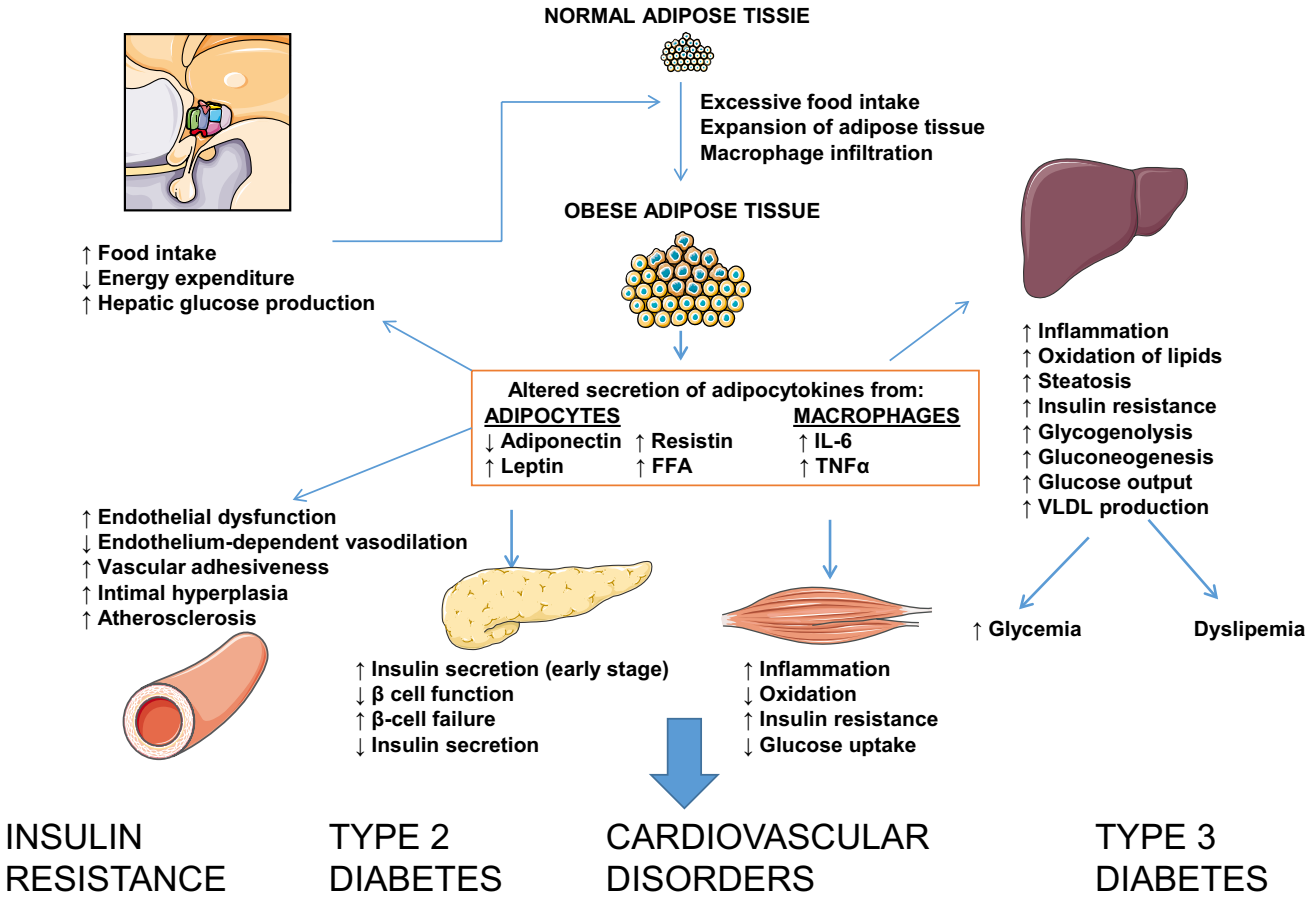

Fig. 1 MS is the consequence of obesity-induced changes in adipocytokine secretion that lead to the development of systemic insulin resistance, type 2 and 3 diabetes mellitus, and cardiovascular disorders. Overnutrition that results from a combination of increased food intake and reduced energy expenditure leads to adipose tissue expansion, increased adipocyte size and number, and increased macrophage infiltration that, together, lead to increased free fatty acid release, dysregulated secretion from adipocytes of a variety of adipocytokines, including adiponectin, leptin, and resistin, and increased release from resident macrophages of the inflammatory cytokines (TNF-α, IL-6). Dysregulated secretion of these adipokines elicits a variety of adverse effects on numerous tissues

This leads to the age-related decline in physiological functions entailing inflammatory damage of cellular proteins, lipids, and DNA. The term "inflammaging" was introduced to underscore the importance of inflammation in senescence and its role in the development of age-related diseases such as MS [33–36]. It entails the slowly progressing, persistent type of oxidative stress resulting from the increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and consequent mitochondrial damage [36–38].

Melatonin and mitochondria

This subject is covered in depth by other reviews in this issue. Melatonin is a powerful scavenger of ROS and RNS, and naturally acts on mitochondria, the site with the highest ROS/RNS production into the cell. Melatonin improves glutathione (GSH) redox cycling and increases GSH content by stimulating its synthesis in the cytoplasm, mitochondria depending on the GSH uptake from cytoplasm to maintain the GSH redox cycling [39]. Finally, melatonin exerts important antiapoptotic effects and most of the apoptotic signals originate from the mitochondria (for ref. see [20, 40, 41].

Melatonin plays an important role in antioxidant defense via the regulation of enzymes involved in the redox pathway and directly through the nonenzymatic, radical scavenger effect that melatonin and some of its metabolites, notably N^1-acetyl-N^2-formyl-5-methoxykynuramine and N^1-acetyl-5-methoxykynuramine, have to scavenge ROS, RNS and organic radicals [42, 43]. Safeguarding of respiratory electron flux, reduction of oxidant formation by lowering electron leakage, and inhibition of mPTP events are among the most important effects on melatonin in mitochondria. Melatonin was reported to protect the mitochondria from oxidative damage in part by preventing cardiolipin oxidation [25, 44].

Melatonin can also act on mitochondrial biogenesis via sirtuins. Sirtuins promote longevity in numerous organisms. The seven mammalian subforms, sirtuin 1 to sirtuin 7, are involved in mitochondrial function. Sirtuins also stimulate mitochondrial biogenesis [45]. Several studies have reported upregulation of sirtuin 1 by melatonin (for ref. see [46, 47]).

Melatonin and inflammation

Counteraction of inflammaging by melatonin occurs at different levels. One of them includes the correction of metabolic dysregulation preventing insulin resistance [48–50]. Among the several regulatory pathways modulated by melatonin treatment (Table 1), the impaired serine phosphorylation of insulin receptor substrate 1 (IRS-1) and concomitant an upregulation of IRS-1 expression may be crucial [51]. Both melatonin and melatonergic agonists (e.g., piromelatine) do counteract the blockade of such a key step in insulin signal transduction [48, 50, 52].

Melatonin also prevents processes that promote inflammation including formation of peroxynitrite and tyrosine nitration by peroxynitrite-derived free radicals [19]. All these changes trigger low-grade inflammation in various organs.

Table 1 Effects of melatonin in animal models of MS

Observation	Reference(s)
Reduced body weight increase and circulating glucose, leptin, and triglycerides in high-fat-fed rats	[53]
Decreased weight gain and plasma insulin and leptin levels in middle-aged rats fed with a high caloric liquid diet	[54]
Normalized glucose tolerance and insulin sensitivity in mice fed with a high-fat diet	[55]
Decreased hyperadiposity in oophorectomized rats	[56–58]
Decreased hyperadiposity in olanzapine-treated rats	[59]
Reduced body weight gain in goldfish	[60]
Normalized body weight increase, glucose tolerance, and insulin sensitivity in rats fed with a high-fat diet (an effect mimicked by the melatonin analog piromelatine)	[52]
Reduced body weight increase and normalized levels and 24 h rhythmicity in circulating insulin, glucose, leptin, adiponectin, triglycerides, and cholesterol	[61]
Anti-inflammatory activity in pancreas and liver of senescence-accelerated prone mice (SAMP8)	[62, 63]
Decreased body weight gain, visceral adiposity, blood insulin, and triglyceride levels and TBARS in rats receiving a high calorie	[64]
Counteracted body weight increase and dyslipidemia and decreased blood pressure (BP) in Zucker diabetic fatty rats	[65]
Improved MS caused by a high fructose intake without affecting food intake in rats	[66–70]
Normalized BP in spontaneously hypertensive rats (an effect mimicked by the melatonin analog piromelatine)	[71]
Improved MS caused by modifying light/dark regimens in rats	[72]
Ameliorated fatty liver in high-fat-fed rats	[73]
When administered during reperfusion, prevented ventricular arrhythmias in hearts from spontaneously hypertensive rats and fructose-fed rats	[74]
Counteracted low-grade inflammation and oxidative stress in Zucker diabetic fatty rats	[75]
Counteracted abnormally high blood levels of glucose and triglycerides, polyphagia, and polydipsia in streptozotocin diabetic rats	[76, 77]
Normalized metabolic and reproductive disturbances in rat´s polycystic ovary syndrome	[78]
Normalized clinical and biochemical parameters of mild inflammation in diet-induced MS in rats	[79]
Normalized hypothalamic gene expression of signals regulating feeding behavior in high-fat fed rats	[80]
Counteracted obesity and abnormal adipokine patterns and metabolism in obese (ob/ob) mice	[81]
Nephroprotective activity in Zucker diabetic fatty rats via inhibition of NADPH oxidase	[82]
Diabetes prevention in high carbohydrate diet-fed rats	[83]
Counteracted abnormal fasting blood glucose, total cholesterol, LDL levels and MDA levels, and ameliorated vascular responses and endothelial dysfunction in diabetic rats	[84]
Augmented tolerance to myocardial ischemia/reperfusion injury in the offspring via restoring cardiac IRS-1/Akt signaling when given to the rat diabetic mother during pregnancy	[85]
Given alone or in combination with metformin improved adiposity, circadian activity, insulin sensitivity, and islet cell failure in rats with diet-induced obesity subjected to circadian disruption	[86]
Via modulation of the MAPK-JNK/P38 signaling pathway, improved nonalcoholic fatty liver disease in obese mice	[87]
In rats subjected to bile duct ligation, counteracted liver apoptosis, and endoplasmic reticulum stress, and mitochondrial dysfunction	[88]
Decreases body weight, liver steatosis, and low-grade inflammation, and improves insulin resistance and gut microbiota in high-fat diet-fed mice	[89]

A third area relevant to inflammaging is that related to melatonin immunological effects. Melatonin's multiple functions entail both proinflammatory and anti-inflammatory actions ("melatonin buffer action" in the immune system) [19, 38, 90]. Melatonin down-regulated proinflammatory cytokines (TNF-α, IL-1β, and IL-6), and up-regulated anti-inflammatory cytokines (e.g., IL-10) in the liver of aged, ovariectomized female rats (an animal model of MS) [91]. In the senescence-accelerated mouse strain SAMP8, decreased levels of TNF-α and IL-1β and increased levels of IL-10 were observed after melatonin treatment in liver [62], pancreas [92], and heart [93].

Peripheral oscillators exist in cells relevant to MS, such as pancreatic β-cells [94], hepatocytes, adipocytes, cardiomyocytes [95], and leukocytes [96, 97]. In all these cell types, melatonin modulates factors involved in metabolic sensing of the circadian apparatus like peroxisome proliferator-activated receptor-γ coactivator-1α, peroxisome proliferator-activated receptor-γ, phosphoinositide 3-kinase, protein kinase B, and the accessory oscillator components AMPK, nicotinamide phosphoribosyl transferase, and sirtuin 1 [38, 98]. Melatonin reduced proinflammatory factors by suppressing the expression of nuclear factor-κB via recruitment of a histone deacetylase to its promoter [99]. Other aspects of epigenetic modulation by melatonin via circadian oscillators have been summarized by [100].

Evidence of melatonin therapeutic value in metabolic syndrome: animal studies

Obesity, type 2 diabetes, and hepatic steatosis ameliorate after melatonin to rats [101, 102]. Melatonin administration normalizes most observed alterations in experimental hyperadiposity concomitantly with improvement of the altered biochemical proinflammatory profile (Table 1).

In streptozotocin-induced type 1 diabetic rats, regeneration and proliferation of β-cells in the pancreas leading to a decrease in blood glucose were observed after melatonin treatment [103], while pinealectomy resulted in hyperinsulinemia and fatty liver [104].

Melatonin treatment improved insulin sensitivity and lipid metabolism in type 2 diabetic rats [105] and increased hepatic glycogen content in the liver [106]. In diabetic mice, melatonin normalized insulin sensitivity and ameliorated hepatic steatosis [107].

Melatonin treatment is effective in reversing hyperadiposity in animal models of MS (Table 1). This occurs in the absence of significant differences in food intake, presumably via increased activity of the sympathetic nervous system innervating white and brown fat [108]. Melatonin was shown to augment the number and activity of brown adipocytes in mammals [109]. Therefore, the gathered experimental data support that melatonin effectively counteracts the disrupting effects seen in diet-induced obesity in animals, in particular, insulin resistance, dyslipidemia, and obesity.

However, it must be noted that most experimental research has been carried out in nocturnal species like rats and mice, which are nocturnal animals, and therefore, care needs to be taken when extrapolating data to humans. In both humans and rodents, melatonin levels rise during the evening, peak in the middle-to-latter half of the night and decline by morning. However, the dark phase is a time of energy expenditure in rodents, coincident with a peak in insulin sensitivity, while in humans, the dark phase is a time of energy deficit or fasting, with elevated glycogen breakdown and gluconeogenesis and decreased insulin sensitivity. These divergences may be even more profound, because melatonin does not only affect physiological functions directly, but also modulates phasing and amplitudes of the circadian master clock and various peripheral circadian oscillators.

Evidence of melatonin therapeutic value in the metabolic syndrome: clinical studies

Table 2 summarizes the results of clinical studies on melatonin activity relevant to human MS. Type 2 diabetic patients have low circulating levels of melatonin [110] with a concurrently and expected upregulation of mRNA expression of melatonin membrane receptor [111]. Furthermore, allelic variants for melatonin receptors were associated with increased levels of fasting blood glucose and/or increased risk of type 2 diabetes [112–114] and with polycystic ovary syndrome [115]. These findings strongly bind melatonin to glucose homeostasis in blood.

Low circulating melatonin levels are found in coronary artery disease [128–131] and this trait was associated with the nondipper pattern of BP in elderly hypertensive individuals [132]. Conversely, the administration of melatonin decreased nocturnal BP in hypertensives [135–138] and normalized age-dependent disturbances of cardiovascular rhythms [139]. A controlled release preparation of 2 mg of melatonin (Circadin®, Neurim) is effective and safe in treating nocturnal hypertension as demonstrated by a meta-analysis of randomized controlled trials [162]. Cardiovascular protection in MS by melatonin could be related to the antihypertensive and anti-remodeling effects of the methoxyindole through its antioxidant and scavenging properties, preserving the availability of nitric oxide and having sympathoplegic effects.

As in experimental animal studies, melatonin administration ameliorates lipid profiles in MS patients. For example, melatonin (1 mg/kg for 30 days) augmented high-density lipoprotein-cholesterol levels in peri- and postmenopausal women [163]. A reduced intestinal absorption of cholesterol [164] or an inhibited cholesterol biosynthesis [165] may explain the hypolipidemic effects of melatonin.

Table 2 Clinical observations on melatonin relevance in MS

Findings	Reference(s)
Low plasma melatonin levels in type 2 diabetic patients	[110, 116–120]
Low plasma melatonin levels in pregnant women with hypertensive or glucose metabolic disorder complications	[121]
Increased number of melatonin receptors in type 2 diabetic patients	[111]
Melatonin receptor gene polymorphism associated with high risk of type 2 diabetes	[112, 122–127]
Genetics of melatonin receptor type 2 is associated with left ventricular function in hypertensive patients and with increased risk of impaired fasting glucose in youth with obesity	[113, 114]
Family association study between melatonin receptor gene polymorphisms and polycystic ovary syndrome	[115]
Low melatonin production in coronary disease independently of β-adrenoceptor blocker treatment	[128–131]
Among elderly hypertensive individuals, nocturnal urinary melatonin excretion is inversely associated with the nondipper pattern	[132]
Melatonin treatment decreases nocturnal BP in type 1 adolescent diabetics	[133, 134]
Melatonin treatment decreases high nocturnal BP in hypertensives	[135–138]
Melatonin administration attenuates age-dependent disturbances of cardiovascular rhythms	[139]
Melatonin treatment prevents catecholamine-induced hypercoagulability in normal volunteers	[140]
Melatonin inhibits human platelet aggregation in vivo and in vitro	[141–143]
Melatonin treatment ameliorates MS in obese patients	[144, 145]
Melatonin treatment improves MS after treatment of bipolar and schizophrenic patients with the second-generation antipsychotics	[146–148]
Melatonin administration normalizes MS in elder hypertensive patients	[149]
Short-term use of prolonged-release melatonin improves sleep maintenance in type 2 diabetic patients with insomnia without affecting glucose and lipid metabolism. Long-term prolonged-release melatonin administration has a beneficial effect on HbA1c, suggesting improved glycemic control	[150]
Melatonin treatment improves enzymatic profile in patients with nonalcoholic liver esteatosis	[151, 152]
The combination of melatonin and zinc acetate, when used alone or in combination with metformin improved glycemic control in type 2 diabetic patients	[153]
Melatonin treatment ameliorated oxidative stress and inflammatory parameters of obese women	[154]
Acute melatonin administration in healthy women impairs glucose tolerance	[155]
The combined administration of melatonin and fluoxetine was effective to treat mood, sleep, and obesity in postmenopausal women	[156]
Increased MTNR1B expression occurred in human islets from risk G-allele carriers. Melatonin treatment in a human recall-by-genotype study reduced insulin secretion and raised glucose levels more extensively in risk G-allele carriers, indicating that an increased melatonin signaling may be a risk factor for type 2 diabetes	[157]
Reduced fat mass and increased lean mass in response to 1 year of melatonin treatment in postmenopausal women	[158]
Evaluation of the efficacy and safety of melatonin for the reduction of reperfusion injury in patients undergoing revascularization for ST-elevation myocardial infarction indicated that intracoronary melatonin administration (median time >3.3 h earlier) was not associated with a reduction in infarct size	[159]
In a post-hoc analysis of the previously reported trial to assess whether the effect of melatonin was affected by the timing of reperfusion, the main finding was that melatonin, when given <2.5 h after symptom onset, did reduce infarct size significantly by approximately 40%	[160]
A prospective nested case-control study of participants from the Nurses' Health Study cohorts I and II indicated that a lower melatonin secretion was significantly associated with a higher risk of myocardial infarct in women with augmented body mass index	[161]

Melatonin treatment prevented the catecholamine-induced hypercoagulability in acute stress that may contribute to the growth of thrombus following rupture of coronary plaque [140]. Inhibition of platelet aggregation by melatonin is also probably involved in this protective effect on atherothrombotic risk in MS [141–143].

The potential therapeutic value of melatonin in MS is supported by several studies including obese patients [144, 145], bipolar and schizophrenic patients treated with the second-generation antipsychotics [146–148], and elder hypertensive patients [149], and improves enzymatic profile in patients with nonalcoholic liver steatosis [151, 152]. In type 2 diabetic patients, the combined administration of melatonin and zinc acetate improved glycemic control when used alone or in combination with metformin [153]. In healthy women included in the Nurses' Health Study cohort, an inverse relationship between urinary 6-sulfatoxy melatonin excretion and insulin levels and insulin

resistance was documented [166]. Collectively, data in Table 2 support that melatonin therapy can be beneficial for patients with MS. However, more studies are needed to identify the appropriate time/duration of treatment/dose relationship administration of melatonin.

It must be noted that several results deny the capacity of melatonin to improve glucose tolerance and to reduce insulin resistance in humans. Melatonin administration decreased glucose tolerance, already in nondiabetic young individuals [166], an observation confirmed by other recent studies [155, 167]. In vitro, melatonin inhibits insulin secretion, an effect that is logical in humans if one presumes that melatonin suppresses insulin during the night to sensitize the pancreatic β-cells in preparation for breakfast, but is more difficult to explain in night-time eating rodents.

Additional information concerning a glucose tolerance-reducing property of melatonin in humans came from the detection of melatonin receptor polymorphisms. To date, several single-nucleotide polymorphisms (SNPs) located near or inside the gene encoding MTNR1B with an association with type 2 diabetes mellitus have been identified in Asian (Indian, Sri Lankan, Chinese, Korean, and Japanese) and European ethnicities [112, 122–127]. Among these SNPs, rs10830963 appears the most strongly associated with an increase in fasting plasma glucose, glucose area under the curve, and glycated hemoglobin (HbA1C), and a decrease in pancreatic β-cell function, basal insulin secretion, and plasma insulin [168]. This G-allele that carries the SNP rs10830963 is prodiabetic and is overexpressed in pancreatic β-cells, causing a more intense decrease in cyclic adenosine monophosphate (cAMP) upon melatonin stimulation and consequently suppressing more strongly the cAMP-dependent secretion of insulin [169]. It appears to affect β-cell function directly and is associated with a defective early insulin response and a decreased β-cell glucose sensitivity [169–171]. In clinical studies, the presence of the G-allele worsens the decrease in glucose tolerance induced by melatonin [172].

The rs10830963 G-allele may have a greater risk on the transition from normal glucose tolerance to prediabetes than on prediabetes to type 2 diabetes mellitus and is thought to have an important influence on glucose levels from childhood onwards [173]. Individuals older than 45 years of age, who are carrying the rs10830963 G-allele, show a higher expression of MTNR1B in pancreatic islets [169]. This has been reported in diabetic rats as well as diabetic humans. It is not known whether this is a physiological adaptive response to reduced melatonin levels or whether it is part of the pathology of diabetes. It has been proposed that an increase in MT_2 receptor expression could increase the inhibitory downstream signaling leading to an overall decrease in insulin release in type 2 diabetes mellitus [169].

Increased MTNR1B expression occurred in human islets from risk G-allele carriers. Melatonin treatment reduced insulin secretion and raised glucose levels more extensively in risk G-allele carriers, indicating that an increased melatonin signaling may be a risk factor for type 2 diabetes [157]. Since the presence of the G-allele was shown to worsen the reduction in glucose tolerance by melatonin [172], strategies of blocking melatonergic signaling in patients with diabetes have been proposed [174].

However, it must be noted that a reduction in insulin secretion is not necessarily associated with insulin resistance in the target organs, clearly improved by melatonin in most studies. In addition, other MT_2 receptor variants with entirely different properties have been found to be also associated with type 2 diabetes. Some of them are entirely dysfunctional because of their incapability of binding melatonin, and others were found to be unable to interact with G_i proteins [175, 176]. Thus, the absence of melatonin signaling is presumably also diabetogenic.

A further important aspect concerns the contrasting findings of impairments of insulin secretion by the overexpressed MT_2 G-allele and the observed reduced melatonin levels in patients with diabetes [110, 116–120]. The reduction in melatonin levels should presumably be considered as a primary change that is associated with the initiation and/or progression of the disease. In fact, the decrease in melatonin has been regarded as a risk factor for type 2 diabetes.

In young adults, the expression levels of the G-allele showed a higher variability, but were not statistically different from those of noncarriers, whereas a strong increase in G-allele expression was observed in individuals above 45 years [169]. Based on these findings, Hardeland recently proposed an aging-related deterioration of the circadian system, which may lead to losses of rhythm amplitudes, presumably also in the pancreatic β-cell oscillators, and additionally to decreases in nocturnal melatonin secretion [47]. This suggestion gives rise to the interesting question on whether exogenous melatonin administered to carriers of the G-allele or to other adults before the age of 40 years might protect the circadian system from losses in amplitudes and, thus, prevent or delay the development of type 2 diabetes. Another important point to consider in human studies is the discrimination of core symptoms (glucose homeostasis) from diabetes-associated pathologies, including those derived from an enhanced oxidative stress like liver steatosis, cardiovascular disease, retinopathy, nephropathy, or osteoporosis. In most of these associated pathologies, melatonin has a demonstrated therapeutic efficacy.

Conclusions

Clinical management of type 2 diabetes includes rigorous lifestyle modifications, insulin therapy, drug treatments that promote insulin sensitization (such as metformin) and insulin secretion (such as glibenclamide), novel glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter 2 inhibitors [177]. These approaches are designed to manage the symptoms of insulin resistance/β-cell dysfunction and are either used alone or in combination. Many drug therapies for diabetes are costly and, in some cases, have been associated with adverse events, including possible pancreatitis, hypoglycemia, and osteoporosis [178]. Thus, there remains a need for new and cost-effective pharmacotherapies for diabetes that have limited additional health risks.

Obesity is a preventable disease, but its prevalence is continuously increasing worldwide, and because it is frequently associated with other cardiovascular risk factors and high mortality, obesity has become an important public health problem and a heavy socioeconomic burden for the overall society. Environmental factors or stressors of the so-called contemporary "24/7" societies have pronounced effects on metabolism producing circadian clock disruption. Furthermore, people whose work involves irregular time schedules and forced exposure to bright light at night (night/shift workers) show significant disruptions in sleep architecture, and increased prevalence of MS. These lines of evidence indicate that the system fails to adjust properly to environmental and/or stressor changes disrupting overall metabolic homeostasis.

The combination of the chronobiotic effect of melatonin with its cytoprotective properties may be an innovative strategy in MS. Type 2 diabetes mellitus and its concomitant oxyradical-mediated damage, inflammation, microvascular disease, and atherothrombotic risk are prevented by melatonin. For example, evaluation of the efficacy and safety of melatonin for the reduction of reperfusion injury in patients undergoing revascularization for ST-elevation myocardial infarction indicated that intracoronary melatonin administration, when given <2.5 h after symptom onset, did reduce infarct size significantly by approximately 40% [160]. Melatonin has a high safety profile and shows a reduced toxicity, thus differing from most many pharmaceutical agents used in MS patients [179].

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 synthesized to treat circadian disorders.

It remains to be established to what extent the new melatonergic agents approved by the US Food and Drug Administration or the European Medicines Agency (ramelteon, agomelatine, and tasimelteon) share a same protective activity as melatonin in MS [180]: for example, ramelteon, when given daily in drinking water (8 mg/kg) for 8 weeks to spontaneously hypertensive male Wistar–Kyoto rats significantly attenuated systolic BP and body weight gain [181]. Likewise, piromelatine, an investigational melatonergic agonist, has been shown to be more effective than melatonin to improve experimental MS [52, 71, 182].

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