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The Role of Melatonin in Chronic Kidney Disease and Its Associated Risk Factors: A New Tool in Our Arsenal?

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Abstract
Background: The increasing incidence of chronic kidney disease (CKD), as a consequence of the high prevalence of arterial hypertension and type 2 diabetes mellitus (T2DM), warrants the need for developing effective treatment approaches. In this regard, the pineal gland-derived hormone melatonin may represent an appealing treatment approach of CKD and its associated risk factors. ***Summary:*** Targeting the adverse pathophysiology surrounding CKD and its associated risk factors has been the concept of pharmacologic treatment developed for its management. This review article aimed to present the role of melatonin in this direction, by providing an overview of melatonin's physiology followed by its effect as a therapeutic agent in arterial hypertension and T2DM. ***Key Messages:*** Melatonin, the primary darkness hormone, possesses pleiotropic mechanisms of action which may have important implications in various pathologic states since its receptors are situated across various organ systems. As a treatment tool in arterial hypertension, melatonin may be efficacious in reducing both daytime and nocturnal blood pressure by influencing endothelial function, oxidative stress, the autonomic nervous system, and the renin-angiotensin system. Melatonin may also increase insulin sensitivity and β-cell function. However, late meal intake may be detrimental in glucose regulation, as consumption close to melatonin peak concentrations may induce hyperglycemia and insulin resistance. This finding may explain the inconsistent glycose regulation achieved with melatonin in clinical trials and meta-analyses. Additionally, the presence of genetic variants to melatonin receptor 2 may predispose to T2DM development. Finally, we present the available preclinical evidence supporting melatonin's efficacy in ameliorating CKD's pathophysiology since melatonin supplementation has not been adequately explored in patients with CKD. The combined use of stem cells with melatonin is an appealing therapeutic approach which ought to be assessed further.

Introduction

Chronic kidney disease (CKD) represents an entity with increasing prevalence across the years, characterized by high morbidity and mortality primarily deriving from cardiovascular causes [1]. The incidence of end-stage renal disease, the most critical form of kidney disease, is also

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expected to increase due to the high prevalence of risk factors for CKD and improved patient care [2]. These trends in the epidemiology of CKD mandate the development of novel therapeutic strategies aiming at its prevention or the attenuation of its progression through controlling its major risk factors, arterial hypertension and type 2 diabetes mellitus (T2DM), which are shared with cardiovascular diseases. In this direction, sodium-glucose cotransporter-2 inhibitors, initially developed to treat T2DM, have revolutionized the treatment of cardiorenal diseases [3]. Moreover, they have recently been endorsed by international societal guidelines, together with the established renin-angiotensin system blockers and the upcoming second-generation aldosterone antagonist finerenone [4].

Melatonin (MT), a hormone produced mainly in the pineal gland but also in most human tissues, may interact with the pathophysiology of kidney diseases and its associated risk factors, as evidenced through experimental and clinical studies. In this narrative review, we focus on the role of MT in these pathologic states and the therapeutic potential of its supplementation.

Physiology of MT

MT is the key hormone produced in response to darkness, initially isolated and described by Lerner et al. [5]. MT is an amphiphilic tryptophan-derived indoleamine with potent antioxidant properties across various tissues and endocrine activities. Its pineal production depends on the suprachiasmatic nucleus, synchronized to the light/dark cycle by the retinal intrinsic photosensitive ganglion cells, which provide the necessary information to the suprachiasmatic nucleus to stimulate this hormone during the dark cycle [6]. Following the receipt of this information, conversion of tryptophan to MT is achieved [7]. Norepinephrine plays an important role in nocturnal MT synthesis through its action on α1b and β1 adrenergic receptors, leading to increases in cyclic adenosine monophosphate and intracellular calcium, thus enhancing arylalkylamine *N*-acetyltransferase activity which mediates the conversion of serotonin to *N*-acetylserotonin [8]. However, a high sympathetic output, as seen in non-dipping hypertension, may stimulate alpha-adrenergic receptors and inhibit the effects mediated by β1-adrenergic receptors, thus preventing MT synthesis.

Subsequent release of MT to the blood and cerebrospinal fluid leads to the widespread availability of this hormone across the central nervous system and the peripheral tissues, potentially being of clinical importance in various disease states. Although the pineal gland is described as the primary site for MT production, MT-synthesizing enzymes have been detected in various tissues and cell types, indicating the extrapineal MT synthesis. It should be noted that under inflammatory conditions, such as arterial hypertension, DM, and CKD, pineal nocturnal MT synthesis is suppressed and its extrapineal production by immune cells is augmented [9].

Despite the substantial scientific research conducted to elucidate MT's pleiotropic effects and role in pathologic states, its physiology and pathophysiology are rather complex and remain incompletely understood. MT is highly prevalent in mitochondria, with its antioxidant action being the most well-characterized [10]. This effect may be directly exerted through the interaction of its indole ring with reactive oxygen and nitrogen species. Thus, the formation of antioxidant metabolites such as cyclic 3-hydroxymelatonin, N1-acetyl-N2-formyl-S-methoxykynuramine, and N1-acetyl-5-methoxykynuramine is promoted. The indirect antioxidant MT action depends on its interaction with MT receptors 1 and 2, which are high-affinity specific G protein-coupled receptors, stimulating the expression and activity of potent antioxidants (superoxide dismutase, catalase, glutathione peroxidase). These receptors are situated across the central nervous system as well as in several organ systems [11]. It is important to note that the G protein-coupled receptor GPR50 heterodimerizes with MT1 and MT2. This might have significant therapeutic implications since the heterodimer GPR50-MT1 is inactive and the binding of agonists to the MT1 protomer is ineffective [12]. No influence of GPR50-MT2 to MT2 function was observed [12].

MT may mediate anti-inflammatory effects through nuclear factor (erythroid-derived 2)-like 2 activation, leading to inhibition of nuclear factor-kappaB and NLRP3 inflammasome activation pathways [13, 14]. Those additional MT effects could ameliorate endothelial cell function [15], which is negatively influenced by inflammatory stimuli [16]. Endothelial cell senescence may also be attenuated by MT through the regulation of telomerase activity, as recently shown [17].

The widespread availability of this hormone influences not only the circadian rhythm but also other aspects of human health and disease, with changes in MT receptor densities and receptor polymorphisms could disrupt MT signaling. Among the involved pathophysiologic states are arterial hypertension, diabetes mellitus, and kidney disease (shown in Fig. 1). These conditions are characterized by accelerated aging mediated by inflammation and oxidative

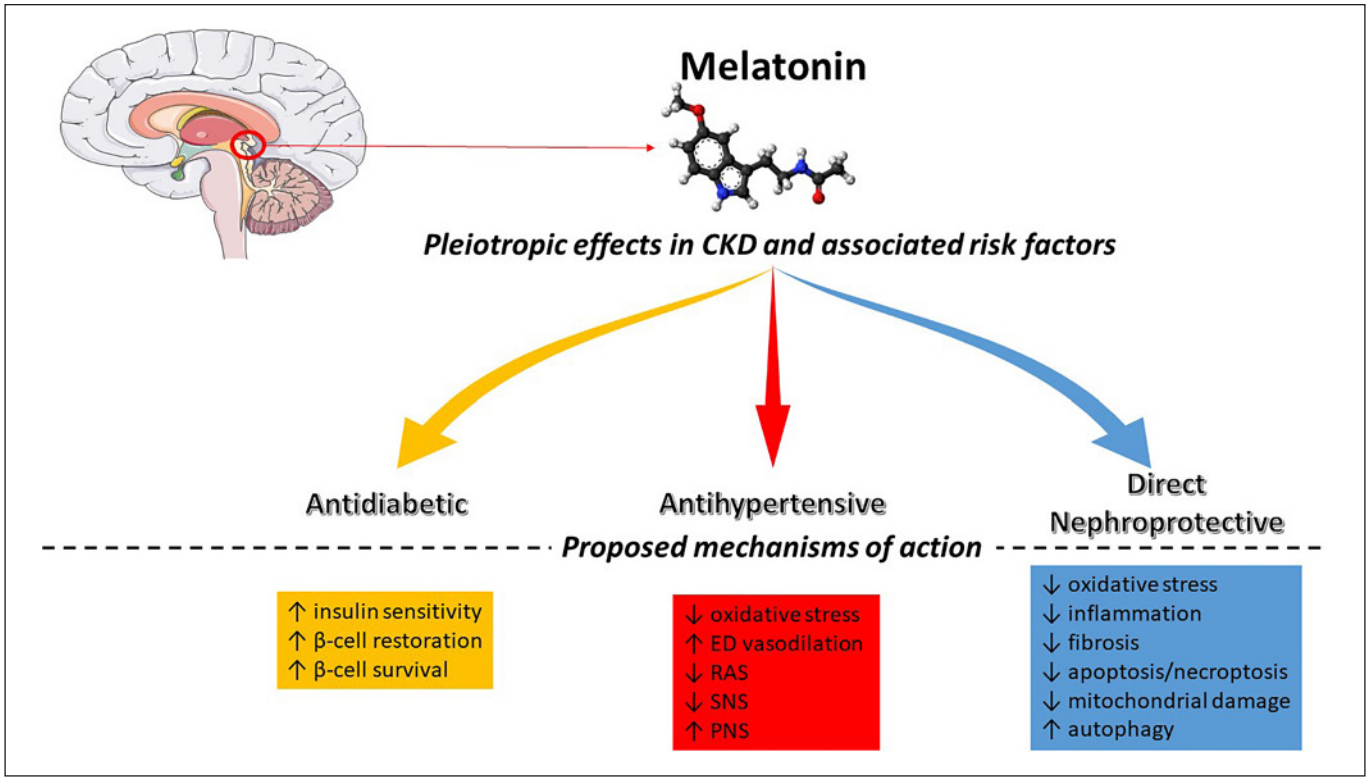

Fig. 1. Pleiotropic effects of MT in CKD and its associated risk factors, together with the proposed mechanisms. CKD, chronic kidney disease; ED, endothelium-dependent; RAS, renin-angiotensin system; SNS, sympathetic nervous system; PNS, parasympathetic nervous system. ↑ indicates stimulation/increase, ↓ indicates inhibition/attenuation.

stress, among others, all of which could potentially be reversed by MT and will be discussed in this review.

MT and Arterial Hypertension

BP-lowering effects have been reported in studies using MT as a treatment approach. Concerning the mechanisms of BP regulation, the antioxidant, anti-inflammatory, and endothelial-protective actions of MT may be responsible [18]. Other than these effects, the interaction of MT with the renin-angiotensin system could represent an additional BP-lowering mechanism [19]. Last but not least, inhibition of the sympathetic nervous system and activation of the parasympathetic nervous system through the decreased release of norepinephrine, glutamate, and serotonin, together with an increased synthesis of gamma aminobutyric acid and acetylcholine, may further promote BP reduction [20–22].

The use of MT as a treatment option for arterial hypertension has been evaluated, especially in cases of nocturnal hypertension, which is associated with adverse cardiovascular outcomes [23]. This is particularly important in CKD since the non-dipping pattern is increasingly prevalent in the CKD and end-stage renal disease populations [24–26]. Nocturnal urinary MT secretion is impaired in non-dippers and was inversely correlated with nocturnal BP, pointing to the potential role of this hormone in BP regulation [27–29]. Thus, nighttime MT supplementation was eventually tried in treatment-naive hypertensive patients, inducing changes of 4 mm Hg and 6 mm Hg in nocturnal systolic and diastolic BP, respectively [30]. The effect was evident after a 3-week treatment protocol instead of a one-time-only administration [30].

Accumulating evidence points to an effect of MT supplementation also in daytime BP. Reduction of both daytime and nocturnal BP was noted following nighttime MT 5 mg in patients with coronary artery disease and

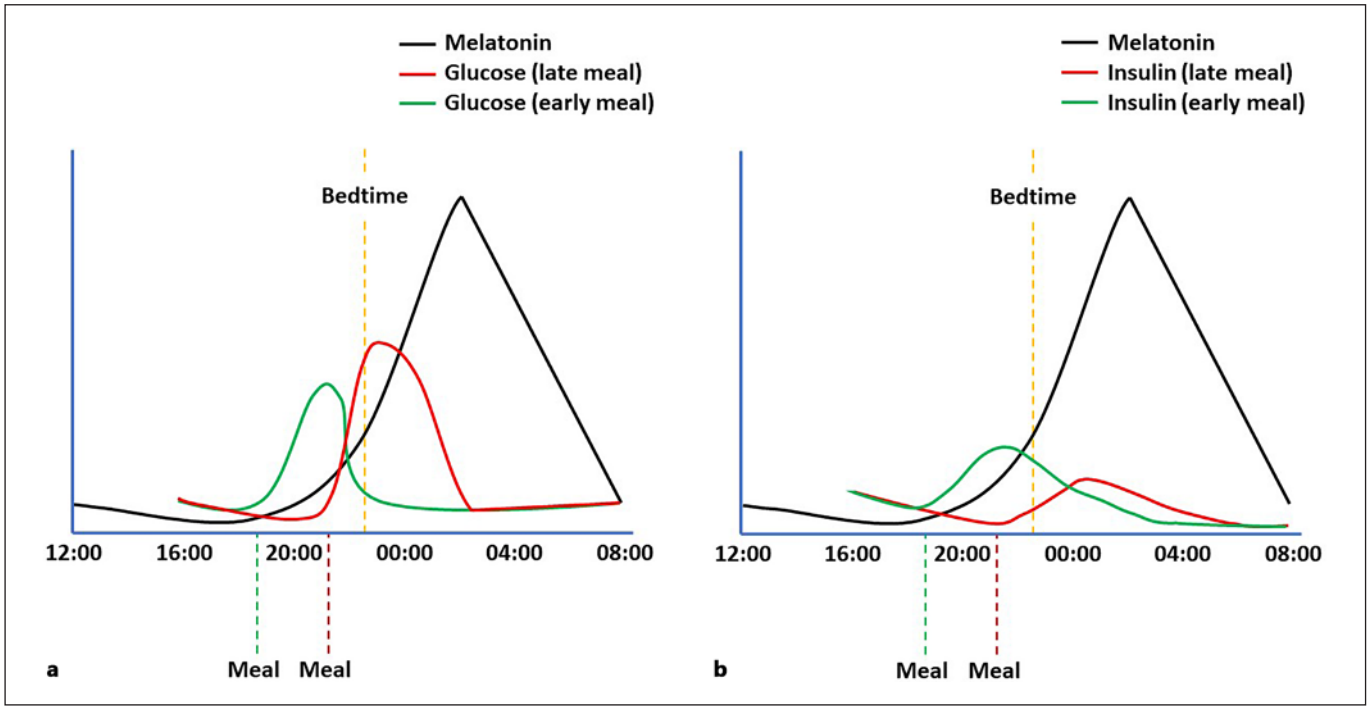

Fig. 2. The effect of MT in glycemia (**a**) and insulin (**b**) secretion according to meal timing. Consuming a meal shortly before MT peaks results in higher glucose levels and reduced insulin secretion.

hypertension with a non-dipping pattern in the study of Rechciński et al. [31]. BP was also reduced in patients with metabolic syndrome, treated for 2 months with nighttime MT 5 mg [32]. In recently completed double-blind, randomized, placebo-controlled trials, MT supplementation led to significant reductions in mean and systolic BP in patients with T2DM with or without coronary artery disease compared to the control group [33, 34]. These studies may have important clinical implications since a potential decrease in daytime BP could represent a valid approach in patients with resistant hypertension [35]. Concerning patients with resistant hypertension and CKD, improvement of sleep quality by adding 3–4 h of sleep through sleep education or sleep medications (including MT) led to a significant BP reduction at 3 months [36]. It should be noted that the BP-lowering effects appear to be generic despite the large dose range, which could be related to an aging-associated malfunction of the neuronal transmission to the pineal gland [37]. It is known that arterial hypertension and CKD are conditions characterized by accelerated, premature aging.

Concerning future directions, adequately designed, large-scale randomized controlled trials ought to be performed to precisely assess the role of MT in BP reduction (daytime and nocturnal). Although most of the available evidence points towards a beneficial effect of MT in the treatment of hypertension, there are areas that should be further explored since coadministration of nighttime MT and nifedipine, a calcium channel blocker, led to a paradoxical increase in systolic and diastolic BP, pointing to the potential interaction of MT with calcium channel signaling as the etiology [38]. Moreover, in a recent randomized controlled trial in African American hypertensives, 4-week 24 mg CR MT did not affect blood pressure parameters [39]. It should be noted that African Americans appear to have lower nocturnal MT secretion, possibly leading to higher nighttime systolic BP values compared to European Americans [40]. Therefore, upcoming studies of MT in hypertension should be aiming to shed light on the potential ethnic disparities and the interaction of MT with calcium channel blockers or even other antihypertensive agents. Additionally, MT's efficacy in specific hypertensive populations, such as those with obstructive sleep apnea and CKD, needs to be evaluated further.

MT and Glucose Homeostasis

T2DM constitutes the most prominent CKD risk factor in the developed world, thus warranting immediate recognition and management. Despite the novel approaches implemented in the treatment of T2DM, its control has declined compared to previous decades [41]. Therefore, it is essential to provide adjunctive treatment options with clinically relevant antidiabetic effects. In this regard, the involvement of MT in insulin secretion and activity has also been characterized. MT, through MT1 and MT2 receptors in pancreatic cells, prevents insulin secretion from β-cells through downregulated cyclic adenosine monophosphate and cyclic guanosine monophosphate, improving their recovery and survival [42]. Thus, MT induces a state of insulin resistance which is, however, essential for daytime insulin sensitivity [43].

Sensitization to insulin-secreting agents and survival of β-cell following the release of MT might be beneficial in patients with pre-existing T2DM [44, 45]. It is, therefore, unsurprising that diminished MT secretion is a risk factor for the development of insulin resistance and T2DM [46, 47]. However, it should be noted that meal timing may be detrimental towards glucose homeostasis, as seen in the case of increased MT concentration in night workers or exogenous MT users who consume meals at these hours of increased MT bioavailability [48]. This hypothesis was further confirmed by a recently reported randomized crossover trial conducted on 845 Spanish late eaters [49]. Garaulet et al. [49] proceeded to administer an oral glucose tolerance test 4 h or 1 h prior to bedtime, stimulating an early and late dinner. Serum MT was significantly higher in the 1-h group, which also featured increased glucose and decreased insulin responses [49]. According to these results, it may be important to avoid meals shortly before bedtime to prevent insulin resistance and hyperglycemia, as shown in Figure 2. Similar recommendations could be made for early morning meals. Early working hours constitute another situation of increased MT concentration, with a small clinical trial demonstrating that early morning food intake resulted in increased postprandial glucose levels [50]. Night work is a special category that should be mentioned. Such individuals could be at increased risk because an additional MT peak is prevalent during daytime sleep, complementary to the anticipated peak at the circadian night, leading to higher 24-h glucose levels [51]. This may partially explain the increased incidence of T2DM in female nurses who work on night shifts [52]. Other than the direct effects on β-cells, the diabetogenic effect of dysregulated MT homeostasis may be related to renal gluconeogenesis, impaired hepatic and adipocyte insulin sensitivity [42].

Recently reported systematic reviews and meta-analyses have not produced identical results, with others pointing towards ameliorated glycemic control and insulin resistance following MT supplementation [53–55], while the study of Lauritzen et al. [56] stresses a potential but not overwhelming effect of MT on those parameters. The impact of meal timing on those effects, which is a critical confounder as mentioned previously, could not be assessed in these studies. This limitation could be applied to previous randomized trials and reported no positive effects of MT on glucose homeostasis since they did not control for dietary patterns [57], or a glucose tolerance test was performed after MT supplementation [58].

T2DM risk has also been associated with variants in the gene coding MT receptor 2 (MTNR1B) [59]. The impaired activation of $G\alpha_{i1}$ and $G\alpha_z$ proteins, together with defective β-arrestin2 recruitment to MT receptor 2 may induce this increased T2DM risk in the carriers of this variant [60]. Several controversial factors need to be further studied in this association, such as the importance of a late chronotype [61, 62]. Additionally, the MTNR1B G-allele carriers exhibited a more impaired β-cell function in the study of Garaulet et al. [49] after being administered with an oral glucose tolerance test close to their bedtime. Despite the presumed association of the MTNR1B gene variant with T2DM, no differences in glycated hemoglobin have been noted in patients with T2DM on antidiabetic treatment carrying the G risk allele in the MTNR1B compared to noncarriers [63]. Regarding clinical endpoints, individuals with T2DM possessing the MTNR1B gene variant had a greater incidence of myocardial infarction in an analysis of the UK Biobank cohort with a 6.8-year follow-up [64]. In contrast, no associations with mortality have been found [65].

MT and CKD

The pleiotropic effects of MT extend to the kidney per se, in addition to its effects on the major CKD risk factors. A plethora of preclinical studies has been conducted in this regard, examining the effect and the mechanisms involved in the protective effect of MT, as shown in Table 1. Despite the numerous preclinical studies examining the importance of MT in CKD, the evidence is scarce in the clinical setting. MT may improve erythropoietin responsiveness through its anti-inflammatory action, thus ameliorating CKD-induced anemia. Moreover, in a recently

Table 1. Overview of preclinical studies assessing the renoprotective mechanisms of MT

Study	Preclinical model	Pathway involved	Mechanism of renoprotective action
Hajam et al. [66]	Wistar rats with DM	NA	Antioxidant
Yoon et al. [67]	P-cresol-treated HPTEC Balb/c mice with CKD	miR-4516/SIAH3/PINK1	Improvement of mitochondrial function Reversal of deleterious mitochondrial morphology and dysregulated dynamics
Aouichat et al. [68]	Zücker diabetic fatty rats	IRE1α/JNK	↓ Endoplasmic reticulum stress Anti-apoptotic
Yoon et al. [69]	P-cresol-treated HPTEC	miR-4516/ITGA9	Anti-fibrotic Inhibition of actin remodeling activation Prevention of cytoskeleton reorganization
Han et al. [70]	High glucose-treated HPTEC	PrP/TGF-β/Smad	Antioxidant Antifibrotic ↓ EndMT
Wei et al. [71]	db/db mice High glucose-treated SV40 MES13 cells	TLR4 TGF-β1/Smad3	Anti-inflammatory Antifibrotic
Li et al. [72]	TGF-β1-treated NRK-49F cells	miR-21-5p/PTEN miR-21-5p/Spry1	Antifibrotic
Kim et al. [73]	TGF-β1-treated NRK-49F cells	TGF-β1	Antioxidant Antifibrotic
Fan et al. [74]	db/db mice	NF-κB TGF-β1/Smad3	Anti-inflammatory Antifibrotic
Ebaid et al. [75]	Wistar rats with DM	NA	Antioxidant
Li et al. [76]	Wild-type mice with DM	AMPK/PGC1α	Antiapoptotic Antifibrotic
Liu et al. [77]	Sprague-Dawley rats with DM	miR-497/ROCK	↓ EndMT
Ji and Xu [78]	Angiotensin II-induced podocytopathy	JAK/STAT	Anti-inflammatory Antiapoptotic

DM, diabetes mellitus; NA, not assessed; HPTEC, human proximal tubular epithelial cell; CKD, chronic kidney disease; SIAH3, Seven in absentia homolog 3; PINK1, Phosphatase and tensin homolog(PTEN)-induced kinase 1; IRE1α, phosphoinositol-requiring enzyme1α; JNK, c-jun amino terminal kinase; ITGA9, Integrin subunit alpha 9; PrP, Prion protein; TGF, Transforming growth factor; EndMT, Endothelial-to-mesenchymal transition; TLR, Toll-like receptor; AMPK, 5'adenosine monophosphate-activated protein kinase; PGC1a, Peroxisome proliferator-activated receptor γ coactivator 1-α; ROCK, Rho-associated kinase; JAK, janus kinase; STAT, Signal transducer and activator of transcription; NF-κB, nuclear factor-kappaB.

reported randomized controlled trial of 60 patients with diabetic kidney disease, nighttime MT 10 mg led to improved glycemic profile and oxidative stress parameters [79]. Similar findings were observed in diabetic patients on maintenance dialysis, who additionally experienced a decline in inflammatory markers [80]. A randomized controlled trial of renal transplant recipients who were administered MT or placebo has also been recently reported, with the group receiving MT experiencing lower levels of neutrophil gelatinase-associated lipocalin, together with reduced levels of inflammatory and oxidative stress markers [81]. However, no studies have been performed assessing the role of MT in disease progression and major cardiorenal outcomes in CKD individuals. Since CKD is a condition characterized by premature aging, it would be interesting to assess the role of MT across the different CKD stages. Moreover, the combination of MT with folic acid also needs to be tested since MT may diminish homocysteine and lead to higher rates of adverse cardiovascular events [82].

With a look to the future, the combination of MT and stem cells could be of particular interest in CKD treatment. MT treatment may prevent uremic toxin-induced mesenchymal stem cell (MSC) senescence via its antioxidant mechanism of action, together with attenuation of pathologic autophagy [83]. Subsequent studies examined the

therapeutic combination of MSC with MT. Initially, Rashed et al. [84] noted that administration of bone marrow-derived MSC pretreated with MT (BMMSC-MT) in a rat model of diabetic nephropathy ameliorated renal function, oxidative stress, fibrosis, and autophagy indices paired with diminished glomerulosclerosis when compared to non-pretreated BMMSC administration. The beneficial effects of BMMSC-MT were further tested in an animal model of unilateral ureteral obstruction-induced CKD, where a significant reduction in TGF-β1 and tumor necrosis factor-alpha paired with a substantial increase in E-cadherin compared to non-pretreated BMMSC were observed, indicating the beneficial impact of this treatment approach in the processes of fibrosis, inflammation, and endothelial-to-mesenchymal transition. These findings were complemented by histological improvement of fibrosis, reversibility of basement membrane disruption, and renal regeneration [85]. The additional effects noted in these studies could be regulated by their higher survivability and the enhanced homing of MT-pretreated MSC to the injured tissue, which may be mediated by matrix metalloproteinase-9, adhesion molecules, and chemokines [85].

Critical evidence has been provided in the study of Yea et al. [86], who assessed the therapeutic potential of exosomes derived from MT-pretreated adipose tissue-derived MSC (ATMSC), named Exocue, in a mouse model of adenine-induced CKD. Compared to control Exocue, administration of MT-Exocue at a dose of 100 μg significantly lowered the expression of genes and circulating markers associated with inflammation and fibrosis. At the same time, CKD-related miR expression was altered considerably in MT-Exocue. Moreover, it ameliorated circulating kidney function markers in a dose-dependent manner, while an improved histological profile characterized by diminished apoptosis and fibrosis was also noted. Lastly, the combination of ATMSC with intraperitoneal MT produced a remarkably downregulated expression of proteins associated with apoptosis, fibrosis, oxidative stress, and mitochondrial damage in a rat model of CKD, together with attenuated renal impairment biomarkers [87]. These were accompanied by a lesser degree of kidney injury and fibrosis upon pathologic examination. However, the lack of an appropriately designed control group (ATMSC, MT) does not allow for adequate quantification of the effect of MT. The action of MT on SC in this study was based on the reduction of oxidative stress, leading to enhanced ATMSC survival and proliferation by the upregulation of the promoting cellular-prior-protein/phosphoinositide 3-kinase/Akt pathway and abrogation of SC senescence [87].

Conclusions

Research on pineal gland-derived MT has provided insightful evidence regarding its protective role in cardiometabolic and renal diseases. Through mainly its pleiotropic effects, MT may be efficacious in managing arterial hypertension, diabetes mellitus, and kidney diseases. However, further understanding of those complex interactions together with precision medicine, through the identification of clinically significant genetic modifications and the seemingly potent combination of stem cells with MT, is essential before implementing MT as a valid treatment option in CKD and its associated risk factors. Perhaps MT's action against inflammation and senescence could be crucial in reversing the pathophysiology of those entities and, through the understanding of endogenous MT at multiple sites, the natural indolamine and its analogs could be used as pharmacological tools.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.T. and A.V. contributed to the design, drafted the work, and gave the final approval of the version to be published. R.G.K. contributed to the conception, revised the work critically, and gave the final approval of the version to be published.

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