Effect of Melatonin Supplementation on Glycemic and Lipid Profiles in Kidney Transplant Recipients: A Clinical Trial

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Keywords. Melatonin; Kidney transplantation; Diabetes mellitus; Blood glucose; Randomized controlled trial

Introduction. Melatonin plays a crucial role in regulating sleep and has potent antioxidant properties. However, the relationship between melatonin supplementation and metabolic factors related to diabetes and lipid profiles—which are associated with increased mortality in kidney transplant recipients has not yet been fully clarified.

Methods. This randomized, double-blind, placebo-controlled trial was conducted at Labbafinejad Hospital, Tehran, Iran. Adult kidney transplant recipients (≥6 months post-transplant) received either 6 mg/day melatonin or placebo for three months. A modified intention-to-treat analysis included 42 patients per group. The primary outcomes were changes in fasting blood sugar (FBS) and HbA1c levels, while secondary outcomes included blood pressure and lipid profile parameters. Between-group effects were estimated using linear regression adjusted for baseline values and confounders.

Results. In the melatonin group, FBS decreased by a median of 6.5 mg/dL ($P < .001$) and HbA1c by 0.25 units ($P < .001$), whereas both parameters increased in the placebo group. The adjusted between-group effect favored melatonin for HbA1c (β = −0.30%; 95% CI: −0.59 to −0.01; $P < .001$) but not for FBS (β = −2.61 mg/dL; 95% CI: −17.93 to 12.71; $P = .283$). Triglyceride levels decreased by 16 mg/dL in the melatonin group compared with an increase of 13.5 mg/dL in the placebo group (adjusted β = −23.77 mg/dL; 95% CI: −45.50 to −2.04; $P = .032$). No significant differences were observed in blood pressure and renal function.

Conclusion. Melatonin supplementation for three months modestly improved glycemic control and lowered serum triglyceride levels in kidney transplant recipients, with no effects on blood pressure or kidney function. These results support melatonin's potential as an adjunct therapy for metabolic dysregulation in this population, warranting further investigation into its long-term benefits.

IJKD 2026;20:234-47
www.ijkd.org

Original Paper

INTRODUCTION

Metabolic complications such as diabetes mellitus, dyslipidemia, hypertension, and obesity are highly prevalent after kidney transplantation and represent a major clinical burden, with significant effects on both patient and graft outcomes.[1] These disorders arise from a multifactorial interplay of immunosuppressive therapy, pre-

existing comorbidities, and lifestyle factors, and their management requires early detection and intervention.[2,3] Safe adjunctive strategies for post-transplant metabolic complications remain clinically important because of their effects on cardiovascular, graft, and patient outcomes.[4]

Melatonin, an indoleamine primarily synthesized in the pineal gland under circadian regulation, has antioxidant and cytoprotective properties that have been investigated in several transplantation-related contexts.[5]

Hyperglycemia increases reactive oxygen species production.[6] The imbalance between intracellular free radicals and antioxidants, along with increased oxidative stress and inflammatory responses, contributes to diabetes-related complications.[7,8] Emerging evidence suggests that melatonin may reduce diabetes-related complications by mitigating oxidative damage.[9]

Beyond its antioxidant effects, melatonin may influence metabolic regulation, although these effects may depend on the timing of administration and individual factors such as *MTNR1B* polymorphisms.[10-13] Its secretion follows a day-night rhythm and may influence insulin secretion and sensitivity and glucagon regulation.[14,15] Some experimental and clinical evidence suggests that melatonin may modulate insulin secretion and insulin sensitivity, although acute suppression of insulin secretion has also been reported, indicating that its metabolic effects should not be considered uniformly beneficial.[16-18] Altered nocturnal melatonin secretion in chronic kidney disease (CKD) may be relevant in kidney transplant recipients.[19]

Despite growing interest in melatonin as a safe and inexpensive adjunctive therapy, evidence regarding its effects on glycemic and lipid parameters in kidney transplant recipients is still limited. This gap is clinically important because transplant recipients are exposed to unique metabolic risks related to immunosuppressive therapy, pre-existing comorbidities, and post-transplant changes in renal function and lifestyle. This study aims to evaluate the efficacy of melatonin in improving diabetes and lipid related parameters in kidney transplant recipients.

MATERIALS AND METHODS

Study design and participants

This study was conducted as a randomized, double-blind, single-center, placebo-controlled clinical trial. It included adult kidney transplant recipients who were at least of six months post-transplantation at the time of study enrollment. The study was performed from January to September 2025 at Labbafinejad Educational, Research, and Medical Center, a referral kidney transplantation center, affiliated with Shahid Beheshti University of Medical Sciences, Tehran, Iran. The ethics Committee review board approved the study protocol (code: IR.SBMU.PHARMACY.REC.1403.163) and the study was performed in accordance with the Declaration of Helsinki. Participation in this study was voluntary and written informed consent was obtained from all patients. The study was approved and received clinical trial approval code from Iranian Registry of Clinical Trials, a primary registry in the World Health Organization Registry Network (IRCT20160412027346N10).

Eligibility criteria were assessed during visits to the outpatient clinic of the medical center. Inclusion criteria were as follows: individuals aged 18 years or older who were willing to provide informed consent, general patients were at least six months post-kidney transplantation at the time of recruitment and agreed not to participate in any other research studies until completion of this study.

Patients were excluded if conditions existed that could compromise the safe implementation of the study protocol, or if they had active infections, malignancies, or chronic liver disease (Child-Pugh classes B and C). Additional exclusion criteria included working night shifts, routine use of melatonin or antioxidant supplements (such as vitamins E and C, coenzyme Q10, or selenium) within the past three months, pregnancy or breastfeeding, a history of cigarette smoking, mood disorders, or medication history involving antidepressants, antipsychotics, antiepileptics, warfarin, or strong CYP1A2 inhibitors. Patients receiving insulin at baseline due to repetitive changes in insulin dose and with a history of hypersensitivity reactions to melatonin or its formulation components were also excluded. Furthermore, any patient hospitalized during the study period was excluded from participation.

Interventions

All eligible participants were randomly assigned

in a 1:1 ratio to either the melatonin group or the placebo group. Participants in the melatonin group received 6 mg of melatonin (two 3 mg tablets manufactured by Razak Pharmaceutical Company, Tehran, Iran) daily at bedtime for three months, while those in the placebo group received two placebo tablets (identical in appearance and also manufactured by Razak Pharmaceutical Company, Tehran, Iran) daily at bedtime for the same duration. Participation in this study did not restrict the use of standard medications. Patients were advised to continue taking their previously prescribed medications as directed and to inform the principal investigator of any changes to their treatment regimen made upon their physician's recommendation. To minimize potential confounding effects on study outcomes, doses of oral antidiabetic medications and lipid-lowering agents remained unchanged throughout the study. With respect to lifestyle-related factors, including diet and physical activity, all patients remained adherent to the comprehensive post-transplant protocol of Labbafinejad Hospital.

Blinding

The study was performed as a double-blind trial. The necessary study medications were provided and packaged uniformly and were undistinguishable. Neither the participants nor the outcome assessors were aware of whether melatonin or placebo is being administered.

Data gathering and follow-up

Demographic data, including name, date of birth, contact number, medication history, and concomitant medical diseases, were collected by investigators from patients before drug administration on the first visit in a face-to-face contact after a written informed consent was obtained. The prepared case report forms were used to collect data of the patients including demographics, baseline clinical and laboratory data. The included patients were followed for three-months. The related clinical data, including systolic and diastolic blood pressures, glucose indices (including fasting blood sugar (FBS) and HbA1c percentage), and lipid profile (including total cholesterol, low-density lipoprotein / high-density lipoprotein and triglyceride level), were recorded at baseline and again three months later at the end of the follow-up period. Adherence to treatment was monitored through telephone follow-ups with patients. Medication was dispensed monthly, and drug consumption was evaluated by counting the remaining pills. After assessment, the medication was reissued to the patient. Adverse effects were evaluated using the Naranjo Adverse Drug Reaction Probability Scale, with a score of 5 or higher considered indicative of a probable side-effects. All patients' tests were performed in the same laboratory.

Outcomes

The primary objective of the study was to evaluate whether melatonin use was associated with improvement in FBS and HbA1c from baseline ($P < .05$). Secondary outcomes included the effects of melatonin on blood pressure and lipid profile.

Sample size estimation

Based on the assumptions from a previous study [12], the mean FBS was considered after 12 weeks of intervention as the primary outcome, with the melatonin group having a mean of 112.1 mg/dL and the placebo group having a mean of 131.4 mg/dL among diabetic patients undergoing hemodialysis. Equal standard deviations of 30 were assumed, Using a two-sided test with a type I error rate of 5% ($\alpha = 0.05$), and a power of 80% ($\beta = 0.2$), along with a potential attrition rate of 20%. Consequently, the sample size was estimated to be 98 patients, with 49 patients in each group using PASS software, version 21.0.3.

Randomization and allocation concealment

The stratified permuted block randomization method was employed to ensure balance in the frequency of antihypertensive medication use (as a potential confounding variable). Blocks were created based on the sample size, with 10 blocks of sizes 4, 6, and 8 used for the group receiving antihypertensive drugs, and 9 blocks of sizes 2, 6 and 8 used for the group not receiving antihypertensive drugs. Randomization was conducted using the "blockrand" package in R software version 4.4.2. Patients were enrolled in each group according to the predetermined sample size and the randomized list, with each individual assigned a unique research code. Each participant was assigned a unique six-digit randomization code, which represented three components: (1) the

participant's antihypertensive medication status for stratification, (2) the treatment allocation (melatonin or placebo), and (3) a participant identifier. Study medications (melatonin and placebo) were labeled only with these six-digit codes, identical to those in the randomization list.

The investigators conducting the trial and all participants were blinded to the meaning of the codes and were unaware of which codes corresponded to melatonin or placebo. Medications were dispensed strictly according to the randomization code sequence. The allocation list linking the codes to treatment groups was securely kept by the independent epidemiologist and remained confidential until completion of data collection and final statistical analysis.

Patients' enrollment

One hundred and thirty-six patients were assessed for eligibility, of which 32 were excluded because they did not meet the study inclusion criteria (less than six months had passed since transplantation). In addition, nine patients declined to participate in the study.

Ninety-five patients were randomized: 47 received placebo and 48 received melatonin. During the study, one patient in the placebo group was lost to follow-up due to migration, two patients were lost to follow-up due to non-attendance, and two patients withdrew because they were unwilling to continue. In the melatonin group, six patients discontinued the study because of drug-related adverse effects, including drowsiness in four patients, facial swelling in one patient, and headache in one patient. Finally, 42 patients in each group were analyzed (Figure1).

Statistical analysis

The data analysis approach in this study was modified Intention-To-Treat (mITT) based on the initial randomization (according to their originally assigned intervention groups). All participants who had baseline assessment after randomization and had post-baseline outcome measurement at the 3-month follow-up were included in the analysis. Participants for whom no post-baseline outcome data were available due to loss to follow-up (e.g., migration) or early discontinuation related to adverse drug events were not included in the final analysis. Exclusions were based on the absence of follow-up data rather than non-adherence to the assigned intervention.

The normality of quantitative data was assessed using Shapiro-Wilk test and histograms. Quantitative data were described using the mean and standard deviation or the median and interquartile range (Q1 – Q3), while qualitative data were described in terms of frequency and percentage. The confidence intervals for medians were calculated using the binomial-based method implemented in Stata's "centile" command, which makes no assumptions about the underlying distribution of the variables. The 95% confidence intervals for the means were estimated using the standard formula. To compare differences in the means of quantitative variables, depending on the normality of the variables, either the parametric Student's t-test or the non-parametric Mann-Whitney U test was utilized. Following the Student's t-test the assumption of equal variances was verified using Levene's test. For assessing differences in the distribution of categorical variables, the chi-square test or Fisher's exact test was employed. To evaluate changes in the factors of interest after the intervention compared to before, either the parametric paired t-test or the non-parametric Wilcoxon signed-rank test was used. To evaluate the adjusted treatment effects, we performed linear regression models for each continuous outcome. For each outcome, the follow-up value was entered as the dependent variable. In Model 1, we adjusted for the treatment group and the corresponding baseline value of the outcome variable. In Model 2, we additionally adjusted for other baseline characteristics (including age, gender, BMI, and other relevant covariates). For outcomes with a non-normal distribution (determined by Shapiro-Wilk test and visual inspection of histograms), log-transformation was applied prior to linear regression analysis. Finally, results are reported as beta coefficients (β) with 95% confidence intervals (CIs). Regarding multiple comparisons, the reported p-values were re-estimated using the Benjamini-Hochberg correction method. This approach helps control the False Discovery Rate (FDR), making it a suitable statistical strategy for evaluating the significance of multiple outcomes. All analyses were performed with a significance level of less than 0.05 using Stata version 17 (StataCorp LLC, College Station, TX 77845, USA).

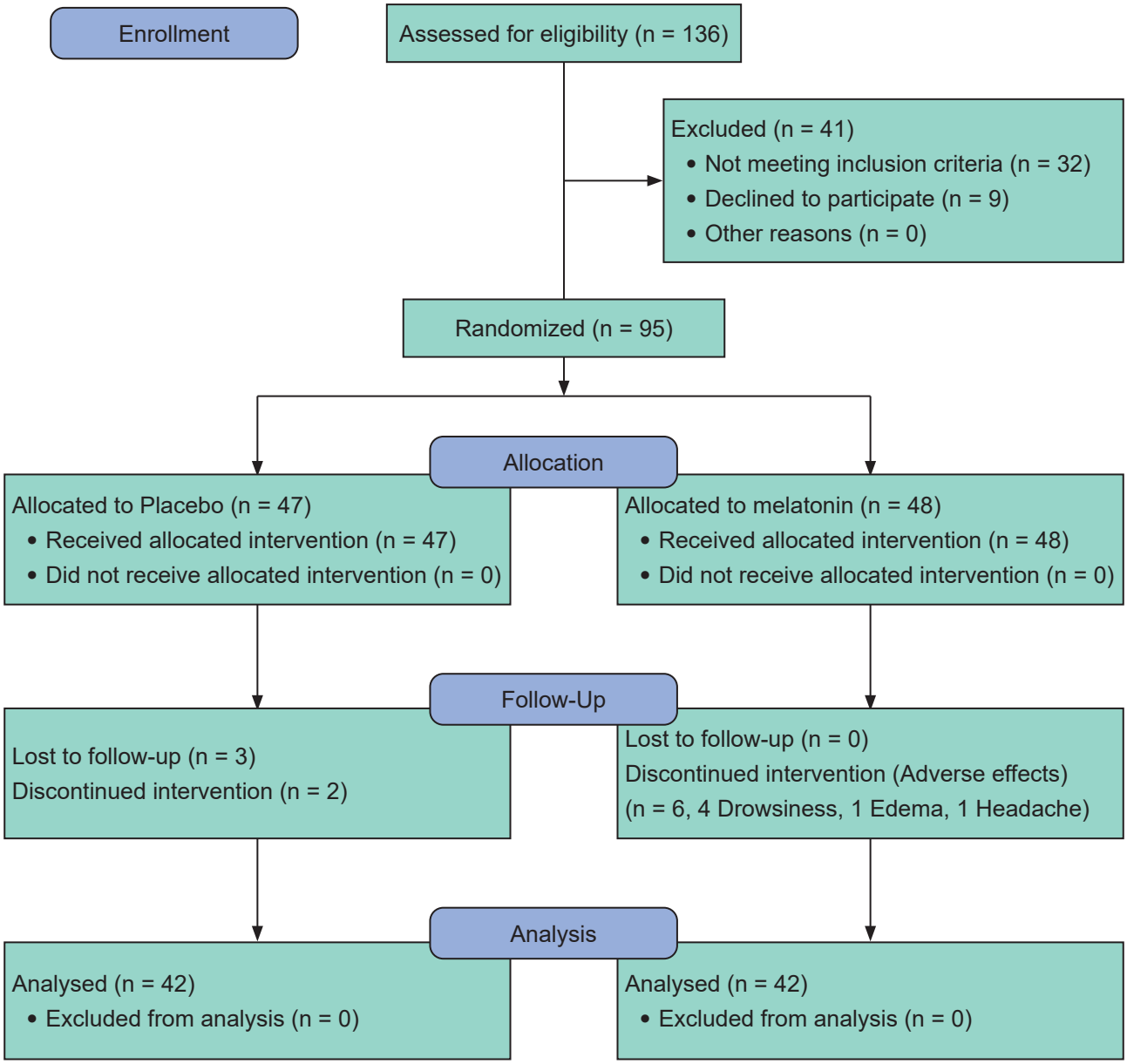

Figure 1. Study consort flow diagram.

RESULTS

One hundred and thirty-six potential patients with a history of kidney transplantation were identified to participate in this study. The CONSORT flow diagram of participants' progress throughout the study is shown in Figure 1. A total of 41 patients were excluded before randomization. After that, 95 patients were randomly allocated (47 patients in group A [placebo] and 48 patients in group B [melatonin]). Ultimately, 42 patients in each group were analyzed using the mITT approach (Figure 1).

According to the results presented in table 1, the demographic and clinical information of the patients was assessed and compared between the two study groups at baseline using mITT approach. In this study, 59.52% of the patients were male. The overall mean age of the patients was 48.47 ± 12.91 years, with no statistically significant difference in age (P = .069) or gender (P = .182) observed between the two study groups. The median time since kidney transplantation among patients was 55 months, with an interquartile range of 17 to 111. Overall, no statistically significant differences were found in the distribution of demographic,

Table 1. Comparison of general and clinical characteristics between the placebo and melatonin groups based on the modified intention-to-treat (mITT) approach

Variables	Placebo (n = 42)	Melatonin (n = 42)	Total (n = 84)	*P*
General information				
Age (Years) (mean ± standard deviation)	50.92 ± 13.20	46.02 ± 12.28	48.47 ± 12.91	.069
Gender (n,%)				
Female	14 (33.33)	20 (47.62)	34 (40.48)	.182
Male	28 (66.67)	22 (52.38)	50 (59.52)	
Height (cm) (mean ± standard deviation)	167.97 ± 10.15	168.92 ± 12.23	168.45 ± 11.18	.341
Weight (kg) (mean ± standard deviation)	69.54 ± 13.04	74.45 ± 12.26	72.0 ± 12.82	.079
Body Mass Index (BMI, kg/m^2) (mean ± standard deviation)	24.57 ± 3.82	26.24 ± 4.55	25.41 ± 4.26	.072
History of diabetes or pre-diabetes (n,%)				
Diabetes	28 (66.67)	25 (59.52)	53 (63.10)	.275
Pre-diabetes	0 (0.0)	3 (7.14)	3 (3.57)	
None	14 (33.33)	14 (33.33)	28 (33.33)	
Hypertension staging (n,%)				
Normal (< 120/ < 80 mmHg)	13 (30.95)	7 (16.67)	20 (23.81)	.493
Elevated (120-129/ < 80 mmHg)	6 (14.29)	8 (19.05)	14 (16.67)	
Stage 1 (130-139/80-89 mmHg)	17 (40.48)	20 (47.62)	37 (44.05)	
Stage 2 (≥ 140/ ≥ 90 mmHg)	6 (14.29)	7 (16.67)	13 (15.48)	
Positive history of dyslipidemia (n,%)	25 (59.52)	31 (73.81)	56 (66.67)	.165
Months passed from transplantation (median (Q1 –Q3))	43.5 (17 – 98)	64.5 (17 – 113)	55 (17 – 111.5)	.809
Drug history (Yes) (n,%)				
Calcineurin inhibitors	41 (97.62)	42 (100.0)	83 (98.81)	1.000
Mycophenolate	42 (100.0)	38 (90.48)	80 (95.24)	.116
mTOR inhibitor	1 (2.38)	4 (9.52)	5 (5.95)	.360
Corticosteroids	42 (100.0)	41 (97.62)	83 (98.81)	1.000
Calcium channel blockers	14 (33.33)	13 (30.95)	27 (32.14)	.815
Beta blockers	21 (50.0)	24 (57.14)	45 (53.57)	.512
ACEi/ARB	17 (40.48)	18 (42.86)	35 (41.67)	.825
Diuretics	6 (14.29)	2 (4.76)	8 (9.52)	.265
Lipid-lowering agents	33 (78.57)	38 (90.48)	71 (84.52)	.227
Anti-diabetic oral agents	14 (33.33)	15 (35.71)	29 (34.52)	.818
Adverse drug events (n,%)**	N = 47	N = 48	N = 95	
Drowsiness and nightmares	0 (0.0)	7 (14.58)	7 (7.37)	.012*
Facial swelling	0 (0.0)	1 (2.08)	1 (1.05)	1.000
Headache	0 (0.0)	1 (2.08)	1 (1.05)	1.000
Constipation	1 (2.13)	0 (0.0)	1 (1.05)	.495

Data presented as mean ± standard deviation or median and interquartile range (Q1-Q3) or frequency and percentage.
mTOR:mammalian target of rapamycin; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers.
*Statistically significant, *P*-value < .05
For continuous variables, p-values were estimated using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. For categorical variables, the Chi-square or Fisher's exact test was used as appropriate.
**Percentages are calculated based on the number of participants after randomization (N = 95)

anthropometric, and clinical and medication history factors between the two study groups ($P > .05$) (Table 1).

Among patients included in the mITT analysis, pill count demonstrated 100% adherence in both groups, as confirmed by telephone follow-ups. To assess adverse drug events (ADEs), all randomized participants were included in the analysis (N = 95). The only adverse event with a statistically significant difference between the melatonin and placebo groups was drowsiness and nightmares ($P = .012$), occurring in 14.58% of the melatonin group versus 0.0% in the placebo group. No significant differences were observed regarding facial swelling, headache, or constipation (Table 1).

A true ITT analysis was performed using all 95 randomized patients (Supplementary Table 1). Baseline triglyceride levels were significantly

Supplementary Table 1. Comparison of general and clinical characteristics between the placebo and melatonin groups based on the intention-to-treat (ITT) approach

Variables	Placebo (n = 47)	Melatonin (n = 48)	Total (n = 95)	*P*
General information				
Age (Years) (mean ± standard deviation)	50.40 ± 13.32	45.56 ± 12.08	47.95 ± 12.88	.066
Gender (n ,%)				
Female	16 (34.04)	21 (43.75)	37 (38.95)	.332
Male	31 (65.96)	27 (56.25)	58 (61.05)	
Height (cm) (mean ± standard deviation)	167.72 ± 9.79	168.79 ± 11.73	168.26 ± 10.76	.294
Weight (kg) (mean ± standard deviation)	69.83 ± 12.82	74.31 ± 13.36	72.09 ± 13.22	.098
Body Mass Index (BMI, kg/m^2) (mean ± standard deviation)	24.79 ± 4.10	26.18 ± 4.65	25.49 ± 4.42	.127
History of diabetes or pre-diabetes (n ,%)				
Diabetics	28 (59.57)	27 (56.25)	55 (57.89)	.768
Pre-diabetics	1 (2.13)	3 (6.25)	4 (4.21)	
None	18 (38.30)	18 (37.50)	36 (37.89)	
Hypertension staging (n ,%)				
Normal (< 120/ < 80 mmHg)	17 (36.17)	9 (18.75)	26 (27.37)	.300
Elevated (120-129/ < 80 mmHg)	8 (17.02)	11 (22.92)	19 (20.0)	
Stage 1 (130-139/80-89 mmHg)	16 (34.04)	21 (43.75)	37 (38.95)	
Stage 2 (≥ 140/ ≥ 90 mmHg)	6 (12.77)	7 (14.58)	13 (13.68)	
Positive history of dyslipidemia (n ,%)	29 (63.04)	34 (70.83)	63 (67.02)	.422
Months passed from transplantation (median (Q1 –Q3))	55 (18 – 146)	60 (17 – 117)	55 (17 – 129)	.785
Drug history (Yes) (n ,%)				
Calcineurin inhibitors	46 (97.87)	47 (97.92)	93 (97.89)	1.000
Mycophenolate	45 (95.74)	44 (91.67)	89 (93.68)	.677
mTOR inhibitor	3 (6.38)	5 (10.42)	8 (8.42)	.714
Corticosteroids	47 (100.0)	47 (97.92)	94 (98.95)	1.000
Calcium channel blockers	15 (31.91)	13 (27.08)	28 (29.47)	.606
Beta blockers	21 (44.68)	25 (52.08)	46 (48.42)	.470
ACEi/ARB	19 (40.43)	22 (45.83)	41 (43.16)	.595
Diuretics	6 (12.77)	2 (4.17)	8 (8.42)	.159
Lipid-lowering agents	35 (74.47)	44 (91.67)	79 (83.16)	.025*
Anti-diabetic oral agents	14 (29.79)	17 (35.42)	31 (32.63)	.558
Hemodynamic and laboratory parameters				
Systolic blood pressure (mmHg) (mean ± standard deviation)	123.09 ± 15.85	125.90 ± 12.89	124.53 ± 14.40	.368
Diastolic blood pressure (mmHg) (mean ± standard deviation)	78.88 ± 8.12	80.75 ± 8.73	79.83 ± 8.44	.307
Serum creatinine (mg/dL) (median (Q1 –Q3))	1.16 (1.04 – 1.45)	1.20 (1.05 – 1.44)	1.19 (1.04 – 1.45)	.893
BUN (mg/dL) (median (Q1 –Q3))	16.35 (12.61 – 22.42)	16.35 (14.01 – 20.48)	16.35 (14.01 – 21.02)	.831
Uric acid (mg/dL) (median (Q1 –Q3))	5.45 (4.40 – 6.40)	5.0 (4.45 – 5.85)	5.15 (4.40 – 6.20)	.288

Supplementary Table 1. Continued

Variables	Placebo (n = 47)	Melatonin (n = 48)	Total (n = 95)	*P*
FBS (mg/dL) (median (Q1 –Q3))	90 (84 – 101)	93 (84.50 – 118.50)	91.50 (84 – 110)	.423
HbA1c (%) (median (Q1 –Q3))	5.90 (5.30 – 6.30)	5.90 (5.40 – 6.50)	5.90 (5.40 – 6.30)	.552
Triglyceride (mg/dL) (median (Q1 –Q3))	140 (85 – 186)	167 (117.50 – 242)	147 (107 – 209)	.020*
Total cholesterol (mg/dL) (median (Q1 –Q3))	157.50 (147 – 181)	153.50 (142 – 184.50)	156.50 (144 – 183)	.830
HDL (mg/dL) (median (Q1 –Q3))	47 (42 – 50)	46 (41.50 – 50)	47 (42 – 50)	.840
LDL (mg/dL) (median (Q1 –Q3))	84.50 (72 – 103)	82 (66.50 – 96)	83 (71 -101)	.676
HDL/LDL ratio (median (Q1 –Q3))	0.52 (0.42 – 0.64)	0.55 (0.44 – 0.64)	0.54 (0.44 – 0.64)	.702

Data presented as mean ± standard deviation or median and interquartile range (Q1-Q3) or frequency and percentage.
*Statistically significant, *P*-value < 0.05
For continuous variables, p-values were estimated using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data.
For categorical variables, the Chi-square or Fisher's exact test was used as appropriate.
mTOR:mammalian target of rapamycin ; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blockers. FBS: Fasting Blood Sugar; BUN: blood urea nitrogen; TG: triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein.

higher in the melatonin group in both ITT and mITT analyses. The use of lipid-lowering agents was higher in the melatonin group in both analyses; however, the difference reached statistical significance only in the ITT analysis (P = .025) and not in the mITT analysis (P = .227), indicating that the significant imbalance in the ITT analysis was related to the excluded patients. Apart from these lipid-related differences, baseline comparability was maintained, and the risk of attrition bias was considered minimal.

Table 2 presents the results of the assessment and comparison of blood pressure levels, laboratory parameters indicative of kidney function, and glycemic and lipid profiles between the melatonin and placebo groups at baseline and three months after intervention. According to the results, only the median and interquartile range of serum triglyceride levels at the beginning of the study differed between the two study groups (P = .006), with a higher median value in the melatonin group compared to the placebo group (median = 174 vs. 136.5 mg/dL). For the other parameters, no statistically significant differences were observed in the parameters distribution between the two study groups at baseline and after three months of intervention (P > .05) (Table 2).

Table 3 presents the results of the assessment of changes in clinical parameters and the differences observed in each parameter three months post-intervention compared to the baseline between the melatonin and placebo groups.

Regarding systolic blood pressure, although the mean systolic BP decreased in the melatonin group about 1.31 mmHg after three months (-1.31 ± 7.10 vs. 0.30 ± 9.73 mmHg in the placebo group), this change was not statistically significant, and the difference observed after three months between the two groups was also not statistically significant (P = .386). Similarly, changes in diastolic blood pressure were not statistically significant in either group (P > .05).

Regarding kidney function, no statistically significant changes were observed in any of the factors such as serum creatinine, BUN, and uric acid between the two groups (P > .05).

Concerning glycemic indices, median FBS decreased significantly in the melatonin group (median = -6.5 mg/dL, IQR = -16, 3, P = .003), compared to the placebo group, which had no

Table 2. Comparison of blood pressure levels, renal performance, glycemic and lipid profiles of patients between intervention groups before and after a three-month intervention based on the modified intention-to-treat (mITT) approach

Factors	Placebo (n = 42, 50%)	Melatonin (n = 42, 50%)	Total (n = 84, 100%)	*P*
Blood pressure levels (mean ± standard deviation)				
SBP (mmHg, before)	123.09 ± 15.85	125.76 ± 13.03	124.42 ± 14.49	.402
SBP (mmHg, after)	123.40 ± 12.07	124.45 ± 10.00	123.92 ± 11.03	.666
DBP (mmHg, before)	78.88 ± 8.12	80.83 ± 8.90	79.85 ± 8.53	.297
DBP (mmHg, after)	79.57 ± 6.92	80.85 ± 6.30	80.21 ± 6.61	.376
Renal function factors (median (Q1 -Q3))				
Serum creatinine (mg/dL, before)	1.16 (1.04 - 1.45)	1.20 (1.08 - 1.47)	1.19 (1.04 - 1.46)	.825
Serum creatinine (mg/dL, after)	1.26 (1.06 - 1.5)	1.28 (1.1 - 1.46)	1.27 (1.08 - 1.46)	.867
BUN (mg/dL, before)	16.35 (12.61 - 22.42)	16.35 (14.01 - 20.56)	16.35 (14.01 - 21.49)	.680
BUN (mg/dL, after)	16.28 (12.14 - 21.49)	15.88 (13.08 - 19.62)	16.54 (13.08 - 20.78)	.604
Uric acid (mg/dL, before)	5.4 (4.4 - 6.3)	5 (4.4 - 6.1)	5.2 (4.4 - 6.15)	.597
Uric acid (mg/dL, after)	4.95 (4.3 - 6)	4.8 (4 - 5.8)	4.9 (4.2 - 5.95)	.603
Glycemic profile (median (Q1 -Q3))				
FBS (mg/dL, before)	91 (83 - 101)	95.5 (85 - 122)	94 (84.5 - 113)	.210
FBS (mg/dL, after)	92 (86 - 103)	94.5 (86- 109)	93 (86 - 107.5)	.860
HbA1c (%, before)	5.9 (5.3 - 6.3)	5.9 (5.4 - 6.5)	5.9 (5.4 - 6.3)	.482
HbA1c (%, after)	5.95 (5.3 - 6.4)	5.7 (5.1 - 6.3)	5.8 (5.1 - 6.35)	.221
Lipid profile (median (Q1 -Q3))				
TG (mg/dL, before)	136.5 (85 - 186)	174 (128 - 246)	147 (102.5 - 210)	.006*
TG (mg/dL, after)	158.5 (109 - 212)	167 (124 - 221)	162 (120.5 - 215)	.418
Total cholesterol (mg/dL, before)	156.5 (144 - 180)	152.5 (141 - 183)	156 (142.5 - 181.5)	.828
Total cholesterol (mg/dL, after)	156 (139 - 172)	156 (134 - 177)	156 (135 - 174.5)	.815
LDL (mg/dL, before)	83 (71 - 101)	81 (65 - 96)	82 (66.5 - 98)	.632
LDL (mg/dL, after)	80 (69 - 96)	79 (64 - 97)	80 (64 - 96.5)	.913
HDL (mg/dL, before)	47 (42 - 50)	45.5 (40 - 49)	46.5 (41 - 49.5)	.516
HDL (mg/dL, after)	46.5 (41 - 49)	44 (41 - 49)	45.5 (41 - 49)	.644
HDL / LDL ratio (before)	0.54 (0.44 - 0.65)	0.55 (0.44- 0.67)	0.55 (0.44 - 0.66)	.913
HDL / LDL ratio (after)	0.57 (0.46 - 0.65)	0.57 (0.47 - 0.68)	0.57 (0.46 - 0.67)	.838

Data presented as mean ± standard deviation or median and interquartile range (Q1-Q3), frequency and percentage
*Statistically significant, *P*-value < .05
For continuous variables, p-values were estimated using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data.
SBP: systolic blood pressure; DBP: Diastolic blood pressure; FBS: Fasting Blood Sugar; BUN: blood urea nitrogen; TG: triglyceride; LDL: low density lipoprotein; HDL: high density lipoprotein.

significant change (median = 3 mg/dL, IQR = -4, 9, $P = .150$). Furthermore, the change in median FBS after three months of intervention between the two groups was statistically significant ($P < .001$). Similar results were observed for HbA1c, where the placebo group experienced a significant increase in median levels after three months of intervention ($P = .016$), while the melatonin group experienced a significant decrease ($P < .001$). Specifically, in the placebo group, the median HbA1c level increased by 0.1% (IQR = -0.1, 0.2), whereas in the melatonin group, the median decreased by 0.25% (IQR = -0.4, -0.1). Additionally, the difference in median HbA1c after three months of intervention between the two groups was statistically significant ($P < .001$).

After assessing changes in the lipid profile of the patients, a statistically significant change was observed only in triglyceride levels in the placebo group ($P < .001$). Although the median triglyceride level in the melatonin group was higher than that in the placebo group at baseline, the placebo group showed an increase, while the melatonin group showed decrease. Specifically, at the end of the study, the median triglyceride level increased by 13.5 mg/dL in the placebo group, while it decreased by 16 mg/dL in the melatonin group. The difference in median triglycerides after three months of intervention between the two groups was statistically significant ($P = .001$). Changes in other lipid profile parameters, such as total cholesterol, LDL, and HDL, were not statistically significant between the two study groups ($P > .05$) (Table 3).

Table 3. Changes in clinical and laboratory parameters of patients after three-month intervention compared to before and its comparison between groups based on the modified intention-to-treat (mITT) approach

Factors	Groups	Difference (After – before)	95% Confidence Interval for differences (95%CI)	Within group (paired) comparison *P*-value[1]	Between group comparison *P*-value[2]	Corrected between group comparison *P*-value[3]
SBP (mmHg) (mean ± standard deviation)	Placebo	0.30 ± 9.73	-2.72, 3.34	.837	.386	.318
	Melatonin	-1.31 ± 7.10	-3.52, 0.90	.239		
DBP (mmHg) (mean ± standard deviation)	Placebo	0.69 ± 7.31	-1.58, 2.97	.544	.668	.556
	Melatonin	0.02 ± 6.86	-2.11, 2.16	.982		
Creatinine (mg/dL) (median (Q1 –Q3))	Placebo	0.02 (-0.04, 0.08)	-0.02, 0.04	.303	.447	.372
	Melatonin	-0.005 (-0.1, 0.05)	-0.04, 0.03	.918		
BUN (mg/dL) (median (Q1 –Q3))	Placebo	-0.43 (-3.27, 1.80)	-2.19, 1.22	.517	.829	.793
	Melatonin	-0.41 (-3.87, 1.87)	-2.71, 0.93	.322		
Uric acid (mg/dL) (median (Q1 –Q3))	Placebo	-0.1 (-0.7, 0.5)	-0.3, 0.2	.328	.609	.507
	Melatonin	-0.1 (-1.0, 0.2)	-0.55, 0.1	.152		
FBS (mg/dL) (median (Q1 –Q3))	Placebo	3 (-4, 9)	-1.85, 5	.150	< .001*	.002*
	Melatonin	-6.5 (-16, 3)	-13.85, -3.14	.003*		
HbA1c (%) (median (Q1 –Q3))	Placebo	0.1 (-0.1, 0.2)	0, 0.2	.016*	< .001*	.002*
	Melatonin	-0.25 (-0.4, -0.1)	-0.3, -0.2	< .001*		
Triglyceride (mg/dL) (median (Q1 –Q3))	Placebo	13.5 (5, 33)	9, 29	< .001*	.001*	.002*
	Melatonin	-16 (-33, 24)	-24.85, 6.28	.285		
Cholesterol (mg/dL) (median (Q1 –Q3))	Placebo	-0.5 (-14, 11)	-8.85, 8	.529	.531	.442
	Melatonin	-5 (-17, 6)	-11.85, 1	.162		
LDL (mg/dL) (median (Q1 –Q3))	Placebo	-3 (-10, 7)	-6, 2.85	.309	.952	.793
	Melatonin	-3.5 (-10, 6)	-7.71, 3.85	.366		
HDL (mg/dL) (median (Q1 –Q3))	Placebo	-1 (-4, 2)	-2, 1	.255	.739	.615
	Melatonin	-1 (-4, 3)	-2, 2	.540		
HDL/LDL ratio (median (Q1 –Q3))	Placebo	0.01 (-0.07, 0.09)	-0.01, 0.06	.603	.876	.730
	Melatonin	0.01 (-0.05, 0.08)	-0.03, 0.06	.358		

Values described as mean ± standard deviation or median and interquartile range (Q1, Q3)
[1]Comparison of before intervention value with after intervention value (paired comparison) based on paired t-test or Wilcoxon signed-rank test
[2]Comparison of difference values between two groups of intervention, based on student's t-test or Mann-Whitney U test
[3]The between group comparison p-values were adjusted for multiplicity using Benjamini-Hochberg correction method
*Statistically significant, *P*-value < .05
SBP: systolic blood pressure; DBP: Diastolic blood pressure; BUN: blood urea nitrogen; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 4 reports the effect of melatonin compared to placebo for each outcome, with adjustments made for baseline measurements and probable confounders (Table 4). Statistical models for each outcome demonstrated a beneficial effect of melatonin compared with placebo after adjusting for probable confounders. The majority of statistical models indicate a protective effect of melatonin compared with placebo, even in cases where the effect size did not reach statistical significance. In models 1 and 2, melatonin supplementation resulted in statistically significant reductions in both HbA1c and triglyceride levels when compared to the placebo group. Specifically, in model 2, the mean HbA1c was 0.30% lower in the melatonin group relative to placebo (ß = -0.30, 95%CI = -0.59, -0.01). Similarly, triglyceride levels decreased by an average of 23.77 mg/dl in the melatonin group compared to placebo (ß = -23.77, 95%CI = -45.50, -2.04). While fasting blood sugar (FBS) levels also exhibited a decrease in the melatonin group, this effect was not statistically significant (ß = -2.61, 95%CI = -17.93, 12.71, *P* = .283).

DISCUSSION

This study aimed to assess the effects of melatonin supplementation on glycemic control and other metabolic parameters in kidney transplant recipients, who are at increased risk for metabolic complications due to immunosuppressive therapy and post-transplant lifestyle changes. Our findings showed that melatonin was associated with a significant reduction in glycated hemoglobin (HbA1c) as shown a favorable effect on triglyceride

Table 4. Adjusted effects of the intervention on study outcomes, controlling for baseline measurements using linear regression models and modified intention-to-treat (mITT) approach

Factors	Groups	Model 1 ß (95%CI)	*P*	Model 2 ß (95%CI)	*P*
SBP (mmHg)	Placebo	Reference	.674	Reference	.274
	Melatonin	-0.60 (-3.45, 2.24)		-1.73 (-4.87, 1.40)	
DBP (mmHg)	Placebo	Reference	.739	Reference	.919
	Melatonin	0.39 (-1.96, 2.75)		0.13 (-2.53, 2.81)	
FBS (mg/dL)	Placebo	Reference	.290	Reference	.283
	Melatonin	-2.12 (-16.16, 11.90)		-2.61 (-17.93, 12.71)	
HbA1c (%)	Placebo	Reference	< .001*	Reference	< .001*
	Melatonin	-0.28 (-0.54, -0.02)		-0.30 (-0.59, -0.01)	
Cholesterol (mg/dL)	Placebo	Reference	.917	Reference	.672
	Melatonin	-0.55 (-10.05, 8.94)		-3.08 (-13.95, 7.78)	
Triglyceride (mg/dL)	Placebo	Reference	.011*	Reference	.032*
	Melatonin	-25.53 (-45.05, -6.009)		-23.77 (-45.50, -2.04)	
HDL (mg/dL)	Placebo	Reference	.647	Reference	.859
	Melatonin	0.26 (-2.23, 2.78)		-0.04 (-2.67, 2.58)	
LDL (mg/dL)	Placebo	Reference	.913	Reference	.683
	Melatonin	-0.01 (-6.93, 6.90)		-2.61 (-10.47, 5.24)	
Creatinine (mg/dL)	Placebo	Reference	.750	Reference	.695
	Melatonin	-0.03 (-0.08, 0.02)		-0.02 (-0.09, 0.04)	
BUN (mg/dL)	Placebo	Reference	.815	Reference	.785
	Melatonin	-0.72 (-3.43, 1.98)		-0.07 (-3.18, 3.03)	
Uric acid (mg/dL)	Placebo	Reference	.794	Reference	.907
	Melatonin	-0.09 (-0.59, 0.39)		0.003 (-0.56, 0.57)	

*Statistically significant, *P*-value < .05
Coefficient (ß), 95% Confidence Interval (95%CI) based on linear regression
Model 1: groups, initial value of each factor
Model 2: groups, initial value of each factor, age, gender, months passed from transplantation, history of pre-diabetes /diabetes, history of dyslipidemia body mass index, drug history (anti-diabetic oral agents, beta blockers, diuretics, ACE/ARB, lipid-lowering agents)

levels. However, the magnitude of these changes was modest, and their clinical relevance should be interpreted cautiously. These findings suggest a potential short-term adjunctive positive metabolic effect of melatonin in kidney transplant recipients.

Melatonin administration was associated with significant improvements in HbA1c compared with placebo, without a significant effect on fasting blood glucose. This finding is consistent with previous evidence suggesting that melatonin may influence glucose metabolism. Ostad mohammadi *et al.* reported similar benefits in patients with type 2 diabetes undergoing hemodialysis, where melatonin supplementation improved insulin sensitivity and glycemic control.[20] Furthermore, a meta-analysis highlighted melatonin's role in glucose homeostasis through its antioxidant and anti-inflammatory properties, suggesting potential benefits in mitigating chronic inflammation and oxidative stress in kidney transplant recipients.[21]

Although HbA1c decreased significantly in the melatonin group, its clinical relevance remains uncertain. Approved antidiabetic medications generally reduce HbA1c by approximately 0.5% to 2.5% when used as monotherapy, with larger effects reported for agents such as glucagon-like peptide-1 receptor agonists and metformin.[22,23] Therefore, the HbA1c change observed in the present study should not be considered comparable to the effects of glucose-lowering medications. Rather, it may indicate a limited short-term adjunctive metabolic effect of melatonin that requires confirmation in larger and longer-term studies.

Furthermore, insulin secretion, insulin resistance, oxidative stress, and inflammatory markers were not assessed in the present study. Therefore, the observed HbA1c change should be interpreted as a clinical finding rather than evidence of a confirmed mechanistic effect.

The mechanisms underlying melatonin's effects on glycemic control are multifactorial. Melatonin receptors are expressed in pancreatic β-cells, where melatonin regulates insulin secretion and protects against β-cell apoptosis.[24] Additionally, melatonin's

antioxidant properties may mitigate oxidative stress-induced insulin resistance, a common complication in kidney transplant recipients due to long-term use of calcineurin inhibitors such as tacrolimus and cyclosporine.[20,25] Our findings highlight melatonin's potential as an adjunctive therapy for improving glycemic outcomes in this population. However, further research is required to fully understand the specific molecular pathways involved.

In addition to its effects on glycemic control, slightly reduced serum triglyceride levels were observed in melatonin group. While baseline triglyceride levels were higher in the melatonin group, the intervention resulted in a median decrease of 16 mg/dL, whereas the placebo group experienced an increase. The triglyceride reduction was modest and should be interpreted cautiously. This finding is consistent with a previous study in which melatonin supplementation reduced triglyceride levels in patients with metabolic syndrome, potentially through modulation of lipoprotein lipase activity and inhibition of hepatic triglyceride synthesis.[26]

Dyslipidemia is a prevalent comorbidity in kidney transplant recipients, often exacerbated by immunosuppressive medications such as corticosteroids and mTOR inhibitors.[3] Elevated triglyceride levels are associated with an increased risk of cardiovascular disease, which remains a leading cause of mortality in this population.[27] In the present study, melatonin was associated with a modest reduction in triglyceride levels; however, the clinical significance of this change remains uncertain, particularly given the baseline difference in triglyceride levels between groups. Therefore, these findings should be interpreted as preliminary rather than evidence supporting melatonin as a lipid-lowering intervention or a strategy to reduce cardiovascular risk in kidney transplant recipients.

No significant differences were observed between the melatonin and placebo groups in kidney function parameters, including serum creatinine and BUN, or in blood pressure levels. These findings suggest that melatonin was not associated with detectable short-term adverse effects on renal function or hemodynamic stability in this study. This observation is consistent with previous reports describing melatonin as generally well tolerated, including in patients with CKD.[28] However, given the limited sample size and short duration of follow-up, these findings should be interpreted as preliminary, and larger studies with longer follow-up and systematic safety monitoring are needed to better establish its safety profile in kidney transplant recipients.

Despite the promising results, several limitations should be acknowledged. First, the relatively short duration of the intervention (three months) may not fully capture the long-term effects of melatonin on metabolic parameters. Future studies with extended follow-up periods are warranted to assess sustained benefits and potential risks. Second, the sample size, although adequately powered for the primary outcome, may limit the generalizability of the findings to broader populations. Due to the lack of similar studies in kidney transplant patients, the closest patient population from other studies was considered for sample size calculation. The analysis was conducted on a mITT population, including only patients who had at least one post-baseline assessment. Although the number of excluded patients was small and balanced between groups, this may limit the generalizability of the results to all randomized participants. Consequently, the primary estimand reflects the treatment effect among patients who could receive (efficacy) and be followed for the intervention, rather than a population-level or policy-level effect (effectiveness).

Additionally, the study population consisted exclusively of kidney transplant recipients, and caution should be applied when extrapolating these results to other patient groups. For example, these results are not generalizable to diabetic kidney transplant recipients who used insulin, as this group was excluded from our study based on the exclusion criteria.

Future research should confirm these findings in larger, longer-term trials with careful adjustment for baseline metabolic risk, assessment of optimal dosing and administration timing, evaluation of potential interactions with immunosuppressive medications, Record lifestyle-related data and systematic safety monitoring. Such studies are needed to determine whether the modest short-term improvements observed in glycemic indices and triglyceride levels translate into clinically meaningful benefits for kidney transplant recipients.

CONCLUSION

In conclusion, our findings indicate that melatonin supplementation is associated with modest improvements in glycemic control and a reduction in triglyceride levels among kidney transplant recipients, all while maintaining renal function and safety. These findings underscore melatonin's potential as an innovative therapeutic agent to mitigate metabolic disturbances in this vulnerable population. By incorporating melatonin into post-transplant care protocols, may help improve metabolic outcomes and alleviate the burden of metabolic complications in kidney transplant recipients.

Acknowledgment

This study was supported via the Labbafinejad hospital, Shahid Beheshti University of Medical Sciences, Iran.

REFERENCES:

1. Liu X, Shen J, Yan H, et al. Posttransplant complications: molecular mechanisms and therapeutic interventions. MedComm. 2024;5(9):e669. DOI: 10.1002/mco2.669
2. Jenssen T, Hartmann A. Post-transplant diabetes mellitus in patients with solid organ transplants. Nat Rev Endocrinol. 2019;15(3):172-88. DOI: 10.1038/s41574-018-0137-7
3. Agarwal A, Prasad GV. Post-transplant dyslipidemia: Mechanisms, diagnosis and management. World J Transplant. 2016;6(1):125-34. DOI: 10.5500/wjt.v6.i1.125
4. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney Int. 2000;57(1):307-13. DOI: 10.1046/j.1523-1755.2000.00816.x
5. Esteban-Zubero E, García-Gil FA, López-Pingarrón L, et al. Potential benefits of melatonin in organ transplantation: a review. J Endocrinol. 2016;229(3):R129-R46. DOI: 10.1530/JOE-16-0117
6. Bondeva T, Wolf G. Reactive oxygen species in diabetic nephropathy: friend or foe? Nephrol Dial Transplant. 2014;29(11):1998-2003. DOI: 10.1093/ndt/gfu037
7. Yan SF, Ramasamy R, Schmidt AM. Mechanisms of disease: advanced glycation end-products and their receptor in inflammation and diabetes complications. Nat Clin Pract Endocrinol Metab. 2008;4(5):285-93. DOI: 10.1038/ncpendmet0786
8. Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. Biomed Pharmacother. 2005;59(7):365-73. DOI: 10.1016/j.biopha.2005.07.002
9. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61(3):253-78. DOI: 10.1111/jpi.12360
10. Rubio-Sastre P, Scheer FA, Gómez-Abellán P, Madrid JA, Garaulet M. Acute melatonin administration in humans impairs glucose tolerance in both the morning and evening. Sleep. 2014;37(10):1715-9. DOI: 10.5665/sleep.4088
11. Gil-Lozano M, Hunter PM, Behan LA, Gladanac B, Casper RF, Brubaker PL. Short-term sleep deprivation with nocturnal light exposure alters time-dependent glucagon-like peptide-1 and insulin secretion in male volunteers. Am J Physiol Endocrinol Metab. 2016;310(1):E41-50. DOI: 10.1152/ajpendo.00298.2015
12. Xia Q, Chen ZX, Wang YC, et al. Association between the melatonin receptor 1B gene polymorphism on the risk of type 2 diabetes, impaired glucose regulation: a meta-analysis. PloS one. 2012;7(11):e50107. DOI: 10.1371/journal.pone.0050107
13. Garaulet M, Qian J, Florez JC, Arendt J, Saxena R, Scheer F. Melatonin Effects on Glucose Metabolism: Time To Unlock the Controversy. Trends Endocrinol Metab. 2020;31(3):192-204. DOI: 10.1016/j.tem.2019.11.011
14. Canteras NS, Ribeiro-Barbosa ER, Goto M, Cipolla-Neto J, Swanson LW. The retinohypothalamic tract: comparison of axonal projection patterns from four major targets. Brain Res Rev. 2011;65(2):150-83. DOI: 10.1016/j.brainresrev.2010.09.006
15. la Fleur SE, Kalsbeek A, Wortel J, van der Vliet J, Buijs RM. Role for the pineal and melatonin in glucose homeostasis: pinealectomy increases night-time glucose concentrations. J Neuroendocrinol. 2001;13(12):1025-32. DOI: 10.1046/j.1365-2826.2001.00717.x
16. Markus RP, Sousa KS, da Silveira Cruz-Machado S, Fernandes PA, Ferreira ZS. Possible Role of Pineal and Extra-Pineal Melatonin in Surveillance, Immunity, and First-Line Defense. Int J Mol Sci. 2021;22(22). DOI: 10.3390/ijms222212143
17. Singh M, Jadhav HR. Melatonin: functions and ligands. Drug Discov Today. 2014;19(9):1410-8. DOI: 10.1016/j.drudis.2014.04.014
18. Picinato MC, Hirata AE, Cipolla-Neto J, et al. Activation of insulin and IGF-1 signaling pathways by melatonin through MT1 receptor in isolated rat pancreatic islets. J Pineal Res. 2008;44(1):88-94. DOI: 10.1111/j.1600-079X.2007.00493.x
19. Rahman A, Hasan AU, Kobori H. Melatonin in chronic kidney disease: a promising chronotherapy targeting the intrarenal renin–angiotensin system. Hypertens Res. 2019;42(6):920-3. DOI: 10.1038/s41440-019-0223-9
20. Ostadmohammadi V, Soleimani A, Bahmani F, et al. The Effects of Melatonin Supplementation on Parameters of Mental Health, Glycemic Control, Markers of Cardiometabolic Risk, and Oxidative Stress in Diabetic Hemodialysis Patients: A Randomized, Double-Blind, Placebo-Controlled Trial. J Ren Nutr. 2020;30(3):242-50. DOI: 10.1053/j.jrn.2019.08.003
21. Theofilis P, Vordoni A, Kalaitzidis RG. The Role of Melatonin in Chronic Kidney Disease and Its Associated Risk Factors: A New Tool in Our Arsenal? Am J Nephrol. 2022;53(7):565-74. DOI: 10.1159/000525441
22. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of

therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes care. 2009;32(1):193-203. DOI: 10.2337/dc08-9025

23. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2024. Diabetes care. 2024;47(Suppl 1):S158-s78. DOI: 10.2337/dc24-er07a
24. Costes S, Boss M, Thomas AP, Matveyenko AV. Activation of Melatonin Signaling Promotes β-Cell Survival and Function. Mol Endocrinol. 2015;29(5):682-92. DOI: 10.1210/me.2014-1293
25. Nath A, Ghosh S, Bandyopadhyay D. Role of melatonin in mitigation of insulin resistance and ensuing diabetic cardiomyopathy. Life Sci. 2024;355:122993. DOI: 10.1016/j.lfs.2024.122993
26. Goyal A, Terry PD, Superak HM, et al. Melatonin supplementation to treat the metabolic syndrome: a randomized controlled trial. Diabetol Metab Syndr. 2014;6(1):124. DOI: 10.1186/1758-5996-6-124
27. Drexel H, Tamargo J, Kaski JC, et al. Triglycerides revisited: is hypertriglyceridaemia a necessary therapeutic target in cardiovascular disease? Eur Heart J Cardiovasc Pharmacother. 2023;9(6):570-82. DOI: 10.1093/ehjcvp/pvad044
28. Markowska M, Niemczyk S, Romejko K. Melatonin Treatment in Kidney Diseases. Cells. 2023;12(6). DOI: 10.3390/cells12060838

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Received February 2026
Revised May 2026
Accepted July 2026