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Research Article

Impact of Melatonin Supplementation on Autonomic Nervous System Function in Adults with Type 2 Diabetes: A Pilot Study

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Abstract

Aims: Health complications with diabetes are numerous, and one of the most life-altering is cardiac autonomic neuropathy. This 4-week pilot investigated whether sympathovagal defects in adults with type 2 diabetes (T2D) may be improved by supplementation with oral melatonin.

Methods: Ten adults (3 male, 7 female) ages 52 - 70 years with T2D and of varying ethnicities, participated in a randomized, double-blinded crossover study, taking 10 mg of melatonin or placebo 30 minutes before bedtime for 4 weeks. Autonomic nervous system (ANS) function, heart rate variability (HRV) measures, ANSAR, sympathetic balance, and sleep quality were assessed via physicals at baseline, 4 and 8 weeks.

Results: Nine subjects exhibited baseline ANS dysfunction and four had abnormal sudomotor function. Valsalva low and high frequency normalized units changed significantly following melatonin supplementation ($p = 0.045$). Systolic blood pressure (SBP) significantly lowered in response to deep breathing and Valsalva after melatonin, and one HRV measure rose in the standing condition. Melatonin enhanced subjective sleep quality.

Conclusion: Beneficial effects on ANS function, including select improvements in HRV measures and decreases in SBP, may result from melatonin supplementation in adults with T2D and ANS dysfunction. Effects on other HRV parameters warrants additional investigation to evaluate dynamic activities like deep breathing and Valsalva maneuvers.

Keywords: ANS Dysfunction; Melatonin; Sleep Quality; Baroreflex Sensitivity

Introduction

Type 2 diabetes (T2D) is characterized by early damage to the autonomic nervous system (ANS), which likely occurs prior to diabetes onset [1]. Such damage frequently results in autonomic neuropathy, with prevalence rates reported as high as 100% [2]. Moreover, ANS dysfunction is the best predictor of sudden death

with intensive glycemic management [3]. A proinflammatory state has been associated with ANS damage in diabetes [4], and sympathovagal imbalance may either result from or be the cause of an increased state of inflammation [4], which plays a key role in the development of both T2D and atherosclerosis. This inflammatory response is controlled by the neural circuitry of the ANS. The afferent arc consists of nerves that sense injury and infection and, in turn, activate a cholinergic anti-inflammatory pathway that modulates the response [5]. The lymphoid organs of the immune system are innervated by cholinergic, catecholaminergic, dopaminergic, and peptidergic neurons, and neurotransmitters can alter the level of function of immune cells. In addition, sensory neurons detect inflammation and can lead to the release of dopamine and norepinephrine, causing depolarization of the vagal sensory fibers and initiation of a motor efferent arc in the brainstem (i.e. the cholinergic anti-inflammatory pathway) [5]. It is the loss of autonomic control with reduction of parasympathetic activity (a hallmark of T2D) that appears to initiate this cascade of inflammatory responses.

One of the most life-altering complications associated with longstanding diabetes is cardiac autonomic neuropathy (CAN) [2,6]. Mortality rates are significantly higher for individuals experiencing CAN compared to others with diabetes without this complication. CAN appears to be related to chronic levels of hyperglycemia, with glycation end products resulting from glycemic elevations playing a significant role in creating inflammation in the microvasculature [4,7,8]. In addition, reduced baroreflex sensitivity (BRS) is associated with hypertension, obesity, T2D [9] and metabolic syndrome [9].

Melatonin has been investigated for its association with the sympathovagal dysfunction in T2D, particularly disordered circadian rhythms [10-12]. Melatonin, a hormone produced by the pineal gland, regulates the circadian rhythmicity orchestrated by the superchiasmatic nucleus [13]. It typically follows a circadian rhythmic profile that peaks during the night, regulating sleep and wake cycles [12,14]. Although melatonin supplements do not always improve sleep quality in older adults [15-17], both sleep and wake cycles are often disturbed in T2D, likely due to impaired melatonin production [18]. Interruptions in normal circadian cycles may add to inflammatory responses and hyperglycemia [19], given that melatonin normally synchronizes the biological clock [11], thereby lowering inflammation [20] and attenuating neurotransmitters of the sympathetic nervous system (SNS) [21,22]. Supplemental melatonin may improve ANS balance, inflammation, oxidative stress, and glycemic management in adults with T2D [11,23,24] and even as little as 0.5 mg can affect circadian rhythm entrainment [25].

Purpose of the Study

The purpose of this pilot study was to investigate whether sympathovagal defects in adults with T2D can be improved or reversed by 10 mg of melatonin supplementation daily for 4 weeks.

Materials and Methods

Subjects

A total of 10 adults of both sexes and varying ethnicities, target age range of 40 - 75 years, with diagnosed T2D were recruited from a local population. Exclusionary criteria included: congestive heart failure, recent myocardial infarction, unstable arrhythmia, any cardiovascular event in the previous year, liver or kidney disease, severe orthostatic hypotension, active tobacco use, type 1 diabetes, hepatitis B or C, presence of HIV, active malignancy in the last year, nighttime shift work, use of melatonin, pregnancy and/or breast-feeding. The study protocol was approved by the Old Dominion University Institutional Research Board and Eastern Virginia Medical School Institutional Research Board. The study was conducted at Eastern Virginia Medical School in a medically supervised research laboratory. Signed and informed consent was obtained from each subject. Study participants were evaluated by a medical professional at each visit (baseline, 4 weeks, and 8 weeks). Potential side effects were recorded for both the placebo and melatonin portions of the study.

Study visits and procedures

This study utilized a single over-the-counter daily dose of melatonin (10 mg) to determine its effect on both autonomic balance and baroreflex sensitivity. Up to 10 mg doses are safe for adults [26]. Individuals were screened by phone as potential candidates for the study utilizing inclusion/exclusion criteria before scheduling volunteers to arrive in a fasted state for a 2-hour appointment at the EVMS Strelitz Diabetes Center in Norfolk, VA. During Visit 1, an inclusion/exclusion form was completed and individuals meeting study requirements were consented into the study prior to proceeding with study procedures. After completing study paperwork at Visit 1, participants then underwent a physical exam by a medical professional. During this visit, height, weight, resting ECG,

and blood pressure (BP) measurements (supine, standing, seated), were recorded. Medication recording, health condition disclosure, basic diabetes screening and a neurological physical were also a part of this evaluation. Heart rate (HR) was evaluated twice each visit for potential tachycardia (90–130 beats per minute) [27]. Participants completed sleep questionnaires and underwent HbA1c measurement via fingerstick (Siemens DCA Vantage 2000 Analyzer), along with Sudoscan, heart rate variability (HRV) and BRS testing. Each of the 3 visits followed the same pattern, with HbA1c testing on visits 1 and 3 and 4-week melatonin or placebo assignment on visits 1 and 2.

Participants were randomly assigned to receive a single 4-week quantity of either melatonin capsules (Life Extension, Ft. Lauderdale, FL) containing 10 mg each or placebo capsules filled with white flour in a double-blinded manner. They were instructed to consume one capsule every evening 30 minutes before bedtime for 4 weeks, and crossover capsules were received on Visit 2 and taken during the second 4-week period. Visit 3 occurred after the second 4-week period. Careful logging of all side effects and events during the study occurred on Visits 2 and 3.

HbA1c testing: A Siemens DCA Vantage 2000 Analyzer [28], DCA Vantage HbA1c test kits, associated medical supplies and universal precautions were utilized for finger-stick testing on visits 1 and 3.

Melatonin: After qualifying for the study and giving their informed consent, subjects were randomly assigned a tablet order. Subjects received a single 4-week quantity of 10 mg melatonin capsules or placebo capsules and were instructed to consume one capsule every evening 30 minutes before bedtime. The crossover dose (melatonin or placebo) was distributed to each subject after 4 weeks and compliance reassessed after the second 4 weeks until each subject had taken both melatonin and placebo. Commercially-produced pure melatonin capsules 135 (Life Extension, Ft. Lauderdale, FL) contained 10 mg each. Placebo capsules contained white flour.

Autonomic nervous system function testing

Before and after each 4-week period, the ANSAR device (ANSAR; ANX 3.0 software; ANSAR Group, Inc., Philadelphia, PA) was utilized to assess systemic (vagal) autonomic function and SNS balance [29]. Subjects underwent three tests of ANS function (measured with R-R intervals): 1) deep breathing (expiratory/inspiratory ratio; E/I); 2) Valsalva maneuver (breath holding); and 3) postural change (standing from sitting). All ANS testing was done at the same time of day both before and after each 4-week supplementation to minimize individual diurnal variations of any residual melatonin following each overnight period.

Power spectral analysis and baroreflex sensitivity testing

Power spectral analysis of HRV was performed using previously validated methods [30] under resting conditions with the ANSAR device for determination of low frequency (LF) and high-frequency (HF) components. The LF component reflects baroreflex function rather than cardiac SNS innervation [31,32], whereas the HF component primarily reflects PNS activity. LF/HF ratios were calculated to provide a measure of ANS balance, along with LF and HF with normalized units. Total spectral power (TSP) was calculated, along with the standard deviation of all normal R-R intervals (SDNN), a measure of both SNS and PNS action on HRV, and the root-mean square of the difference of successive R-R intervals (RMSSD), a measure primarily of PNS activity [33]. All power spectral analyses were conducted at baseline and again after each 4-week supplementation.

Spontaneous sensitivity of the baroreceptor-HR reflex time domain and frequency domain techniques was measured with the ANSAR device using validated methods [27,30]. Sudoscan (Aspire Medical Solutions, NY) testing was also used to quantify changes in sudomotor and small nerve fiber function (i.e. peripheral SNS tone) and, together with BRS, to determine PNS balance.

Sleep quality

To account for any possible effects of sleep quality alone due to melatonin supplementation, subjects completed the Pittsburgh Sleep Quality Index (PSQI) [34,35], a validated, self-rated questionnaire assessing sleep quality and disturbances over a 1-month time interval, before and after each 4-week period. This index includes seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction.

Data analyses

Repeated measures analysis of variance (ANOVA) was used to compare pre- and post-supplementation values for melatonin and placebo. Data were normalized. Relationships among ANS function, BRS, sleep quality measures, and melatonin dose were determined with Spearman's partial correlations. Friedman's ANOVA

was employed for non-normally distributed data. Comparison of ANS assessment variables was performed after age and HbA1c adjustment [36]. The level of significance for all analyses was set at $p < 0.05$.

Results

Participants (3 male, 7 female) ranged in age from 52 to 70 years (62.8 ± 6.0 years). Their body weight was 218.3 ± 31.1 pounds. All (but one) were obese with body mass indexes ranging from 28.7 to 47.0 (mean of 36.4 ± 5.5 for obese subjects). Baseline HbA1c values (7.0 ± 0.9%) did not change significantly over 8 weeks, regardless of the supplementation order. The lone side effect reported during melatonin supplementation was sleepiness, reported by one subject.

Autonomic function and power spectral analysis

Nine of 10 participants presented with initial ANS dysfunction, ranging from mild to advanced, with one of the nine with likely sympathetic withdrawal. Four of these individuals also had abnormal sudomotor function, further validating ANSAR findings. Only one participant presented with no evidence of dysfunction at baseline. No participants exhibited orthostatic hypotension, even though this measure was tested twice each visit with ANSAR BP testing of positional changes from seated to standing and from lying to standing. Likewise, none experienced tachycardia, or even notable HR elevations, throughout testing. All participants were within a normal or slightly bradycardic HR range at baseline and both subsequent visits.

Spearman's partial correlations accounted for differences in age and HbA1c , and key correlations are in Table 1. Friedman's ANOVA tests were run for E/I Ratio, Valsalva Ratio, 30:15 Ratio, and all HRV variables. Ratio testing showed no significant changes with supplementation. Analysis of power spectral analysis components revealed no differences at any time point. However, individual evaluation of frequency domain components revealed that Valsalva LF (n.u) was significantly different ($p = 0.045$), and pairwise comparisons (Table 2) revealed significant differences between baseline and melatonin ($p = 0.042$), but not between baseline and placebo ($p = 0.353$) or placebo and melatonin ($p = 0.371$). Likewise, Valsalva HF (n.u) was different between the baseline, placebo and melatonin conditions ($p = 0.045$), seen between baseline and melatonin conditions ($p = 0.042$), but not baseline and placebo ($p = 0.353$) or placebo and melatonin ($p = 0.371$).

Variable	Correlation/Significance Value
Melatonin Valsalva LF/HF	Melatonin Valsalva LF (n.u) .976, p =0.000 Melatonin Valsalva HF (n.u) -.976, p =0.000
Melatonin Valsalva TSP	Time Domain SDNN Baseline .693, p =0.026 Time Domain SDNN Placebo .729, p =0.017 Time Domain SDNN Melatonin .891, p =0.001
Placebo Valsalva TSP	Time Domain RMSSD Baseline .697, p =0.025 Time Domain RMSSD Placebo .867, p =0.001 Time Domain RMSSD Melatonin .745, p =0.013

Table 1: Spearman's partial correlations.

LF: Low Frequency; HF: High Frequency; (n.u): Normalized Units; TSP: Total Spectral Power; SDNN: Standard Deviation of NN Intervals; RMSSD: Root-Mean Square of the Difference.

Standing SDNN, a time domain component, was significantly higher in the melatonin measurement ($p = 0.032$) than baseline or placebo. Pairwise comparisons revealed significant differences between placebo and melatonin ($p = 0.042$), but not between baseline and placebo ($p = 0.371$) or baseline and melatonin ($p = 0.353$). There were no other significant interactions relating to time domain variables.

Baroreflex sensitivity

BP and HR responses were examined across all three conditions (deep breathing, Valsalva, 30:15 Ratio). HR did not significantly differ; however, melatonin supplementation was associated with significantly lower systolic BP responses during deep breathing [X^2 (2, N = 10) = 6.821, $p = 0.033$] and Valsalva [X^2 (2, N = 10) = 7.947, $p = 0.019$] testing.

A one-way repeated measures ANOVA examined differences in Sudoscan results at baseline, and after placebo and melatonin conditions. There were no outliers and data were normally distributed. There were no changes in the conditions over time, $F (2,18) = 0.055$, $p = 0.844$, $\eta^2 = 0.006$ or differences between condition means at the different time points ($p > 0.05$).

Variables and Comparisons	Rank			Test Statistics			
Valsalva	**Baseline**	**Placebo**	**Melatonin**	**N**	**Sig.**	**Test Statistic**	**DOF**
LF nu	1.400	2.100	2.500	10	*0.045	6.200	2
Pairwise Comparisons	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**N**	**Sig.**	**Adj. Sig.**	
Baseline/Placebo	-0.700	0.447	-1.565	10	0.118	0.353	
Baseline/Mel	-1.100	0.447	-2.46	10	0.014	*0.042	
Placebo/Melatonin	-0.400	0.447	-0.894	10	0.371	1.000	
Valsalva	**Baseline**	**Placebo**	**Melatonin**	**N**	**Sig.**	**Test Statistic**	**DOF**
HF nu	2.600	1.900	1.500	10	*0.045	6.200	2
Pairwise Comparisons	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**N**	**Sig.**	**Adj. Sig.**	
Melatonin/Placebo	0.400	0.447	0.894	10	0.371	1.000	
Baseline/Melatonin	1.100	0.447	2.46	10	0.014	*0.042	
Placebo/Baseline	0.700	0.447	1.565	10	0.118	0.353	
30:15	**Baseline**	**Placebo**	**Melatonin**	**N**	**Sig.**	**Test Statistic**	**DOF**
SDNN	1.900	1.500	2.600	10	*0.032	6.889	2
Pairwise Comparisons	**Test Statistic**	**Std. Error**	**Std. Test Statistic**	**N**	**Sig.**	**Adj. Sig.**	
Baseline/Placebo	0.400	0.447	0.894	10	0.371	1.000	
Placebo/Melatonin	-1.100	0.447	-2.46	10	0.014	*0.042	
Baseline/Melatonin	-0.700	0.447	-1.565	10	0.118	0.353	

Table 2: Log10 transformed nonparametric pairwise comparisons.

*Significance level is set at 0.05.

Sleep quality

Median Sleep Quality scores were generated for all sleep components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medication, daytime dysfunction, and global PSQI. Subjective sleep quality scores were significantly different between the baseline, placebo and melatonin scores, X^2 (3, N = 10) = 12.929, p = 0.002. Post hoc analysis revealed statistically differences in SSQ scores from placebo to melatonin ($p < 0.011$). An evaluation of subjective sleep quality revealed significant differences between the groups ($p < 0.002$) (Table 3). There were no other statistically significant differences found in these measures.

Discussion

This study examined the impact of oral supplementation with 10 mg of melatonin daily 30 minutes prior to bedtime for four weeks to determine its impact on ANS function in adults with T2D. We hypothesized that the ANS dysfunction in T2D, which causes a neuroinflammatory response and ANS impairment, would improve as the result of melatonin supplementation. We found that oral supplementation significantly improved select measures of ANS function, including increasing HRV variables of normalized units of LF and HF during the Valsalva portion of ANSAR testing only; lowering SBP responses during deep breathing and Valsalva (both measuring BRS); and improving subjective sleep quality. We had hypothesized that ANS function would improve with melatonin supplementation, and this was found to be partly true for the study participants. However, power spectral measures, such as LF, representing a balance of both parasympathetic and sympathetic activity, and HF, a reflection of parasympathetic balance, did not significantly change across any of our testing conditions despite changes in other measures.

	Mean Rank			Test Statistics			
	Base-line	Placebo	Melato-nin	N	Sig.	Test Statistic	DOF
Sleep Questionnaire							
Subjective Sleep Quality	1.800	1.450	2.750	10	*0.002	12.929	2
Sleep Latency	2.200	2.100	1.790	10	0.393	1.867	2
Sleep Duration	1.850	1.850	2.300	10	0.368	2	2
Sleep Efficiency	1.750	2.250	2.000	10	0.210	3.125	2
Sleep Distur-bances	2.000	2.000	2.000	10	1.000	0.000	2
Sleep Medication	1.700	2.000	2.300	10	0.135	4.000	2
Daytime Dysfunction	2,25	1.900	1.850	10	0.368	2.000	2
Global PSQI	2.400	1.850	1.750	10	0.130	4.083	2

Table 3: Friedman's ANOVA sleep questionnaire results.

*$p < 0.05$; PSQI: Pittsburgh Sleep Quality Index.

The interpretation of HRV variables like LF and HF is an ongoing debate [37,38] and should not be confused with HRV components with normalized units, such as LF (n.u) and HF (n.u) [39]. Undoubtedly, the arterial baroreflex is an important determinant of the neural regulation of the cardiovascular system; baroreceptors perceive stretch in the aorta with increasing BP and send signals via the vagus nerve. However, coordinated firing of both ANS arms is necessary to respond fully to changes in BP. Baroreflex-mediated sympathoexcitation contributes to the development and progression of many cardiovascular disorders; thus, the quantitative estimation of the arterial baroreceptor-heart rate reflex (i.e. BRS), is now regarded as a synthetic index of neural regulation at the sinus atrial node [30]. In fact, LF power likely reflects baroreflex function, not cardiac SNS innervation [31,32]. Theoretically, normalized LF and HF variables may be extremely similar, but they likely better represent a continuum of outcomes or potential changes that happen over a period and small deviations of measurement rather than two separate variables [37]. During a dynamic activity, such as a Valsalva maneuver where a continuum applies, only one specific reading is evaluated with LF and HF or LF/HF, suggesting that relying on normalized unit may be warranted. Viewed collectively with improvements in HF (n.u) and LF (n.u) in this study, they become of greater interest since we also found a positive effect on lowering SBP during that and other activities with melatonin supplementation.

Abnormal Q-T interval, DBP, and elevated resting HR values were not observed in this study. However, SDNN, a time domain component representing the standard deviation of normal RR intervals, rose in the standing condition in our adults with T2D. Conversely, Subbalakshmi., *et al*. Subbalakshmi, Adhikari [40] investigated correlates of SDNN in T2D and found that higher heart rates, DBP, and Q-T dysfunction were related to a reduction in SDNN in such individuals, and abnormalities in SDNN and RMSSD precede inflammation in adults with newly-diagnosed T2D [4]. Depressed or lowered values of SDNN have been associated with increases in risk of sudden death, particularly in adults with known heart issues. Previous research indicates that E:I Ratio and SDNN are valid markers for monitoring CAN, yet we found no significant differences in the ratios across conditions [41]. Our findings, therefore, suggest a potential positive effect of melatonin supplementation on SDNN, as least in response to standing. All our participants were overweight or obese and most were taking prescribed BP lowering medications. HRV parameters have been researched in similar cohorts with nonsignificant findings; however, individuals with overweight or obesity may benefit from melatonin supplementation to potentially increase SDNN before more extreme dysfunction occurs [42].

BRS in this study was unchanged, indicating that vagal cardiac activity most likely did not vary with HR. Under resting conditions, vagal tone prevails and variations in heart rate are largely dependent on vagal modulation. Some participants experienced mild bradycardia (HR of 58/59) during rest, indicating higher PNS tone and possible SNS withdrawal. Of interest, SBP did change in relationship to deep breathing and Valsalva; placebo group SBP rose higher in comparison to baseline in both conditions, whereas the melatonin group SBP was significantly lower, moving the opposite direction. Although we cannot fully reconcile these findings during placebo supplementation, it appears that melatonin had a positive effect. Our results are similar to other BP research with adults with type 1 diabetes using ambulatory BP monitors who also took 10

mg of melatonin daily [43]. That study documented decreases in SBP during sleep and while ours were only during awake conditions.

Even though Sudoscan measures assess small fiber and ANS activity (baroreflex) was unchanged, this device is valid and useful for measuring sudomotor changes at the microvascular level [44]. Casellini et al. [45] used Sudoscan to detect peripheral neuropathy, and Gandhi., *et al*. [46] used a similar device to detect peripheral distal neuropathy and CAN in older adults with T2D, finding it most effective for detecting peripheral changes. Unsurprisingly, our results suggest that supplementing with 10 mg of melatonin daily did not result in measurable small fiber and baroreflex changes, although the potential effects of longer supplementation or different doses were not evaluated.

Subjective sleep quality significantly improved in this study between the baseline and melatonin conditions, with 80% of participants reporting improvements likely related to melatonin supplementation since they were unaware of which capsules they were taking during each 4-week period. Changes in other sleep measures (e.g. sleep latency, daytime dysfunction, global PSQI) with melatonin supplementation were not statistically significant. Similar research has indicated positive results in various PSQI sleep scores in adults supplementing with 4 mg of melatonin one hour before bedtime over a 21-day time period, which differs from our methodology of administering 10 mg 30 minutes prior to bedtime for 4 weeks [35]. It is possible that for older adults with T2D, either inclusion of a larger group of subjects or undertaking a longer period of melatonin supplementation may have resulted in significant positive changes in other sleep measures.

How melatonin is used and orchestrated within the human brain and body can also be affected by medication usage. Participants in the current study had myriad health comorbidities and took numerous prescribed medications. Use of SSRIs to treat depression is common in T2D, with possible brain interactions. BP medications have varying interactions with melatonin, as melatonin has been found to lower BP nocturnally in beneficial ways, and NSAIDs are known to reduce the efficacy of or suppress melatonin synthesis, which may have contributed to a type II error in our study [47-50]. This pilot study was not designed to account for potential effects of other medications by participants, although individuals with major psychotic conditions were excluded from participation. Thus, the potential exists that some of their other medications may have impacted the potential effects of supplemental melatonin.

This pilot study has additional limitations, such as use of HbA1c values as an indicator of overall glycemic management, which may not be ideal for individuals with CAN. While compliance with supplement use was monitored, participants were reminded and then trusted to comply with instructions about supplement timing. Future research should consider incorporating melatonin supplementation in T2D with 24-hr halter monitors to capture a range of values and continuums to evaluate sleep and activities of daily living, paired with clinically controlled ANSAR testing protocols. Additionally, inclusion of a larger number of participants with stricter medication parameters and a longer trial, such as 8 or more weeks with 10 mg of daily melatonin, may also more effectively evaluate its potential effects.

Conclusion

Beneficial effects on autonomic nervous system function, such as select improvements in SDNN HRV measures and decreases in SBP during deep breathing and Valsalva maneuvers, may result from supplementation with 10 mg of melatonin 30 min before bedtime over a 4-week period in adults with T2D and some CAN dysfunction. Its demonstrated effect on other HRV parameters (LF and HF, normalized) warrants additional evaluation during dynamic activities like Valsalva maneuvers. Its positive impact on sleep quality is promising but more research on the effects of different doses over longer periods of time and accounting for use of other prescribed medications is warranted. Future research should examine the potential impact of melatonin in adults with T2D with normal BP and HR status to determine how protective mechanisms may be developed in this population.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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