

Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study

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Background: Diabetes is a major comorbidity in insomnia patients. The efficacy and safety of prolonged-release melatonin 2 mg in the treatment of glucose, lipid metabolism, and sleep was studied in 36 type 2 diabetic patients with insomnia (11 men, 25 women, age 46–77 years).

Methods: In a randomized, double-blind, crossover study, the subjects were treated for 3 weeks (period 1) with prolonged-release melatonin or placebo, followed by a one-week washout period, and then crossed over for another 3 weeks (period 2) of treatment with the other preparation. All tablets were taken 2 hours before bedtime for a period of 3 weeks. In an extension period of 5 months, prolonged-release melatonin was given nightly to all patients in an open-label design. Sleep was objectively monitored in a subgroup of 22 patients using wrist actigraphy. Fasting glucose, fructosamine, insulin, C-peptide, triglycerides, total cholesterol, high-density and low-density lipoprotein cholesterol, and some antioxidants, as well as glycosylated hemoglobin (HbA1c) levels were measured at baseline and at the end of the study. All concomitant medications were continued throughout the study.

Results: No significant changes in serum glucose, fructosamine, insulin, C-peptide, antioxidant levels or blood chemistry were observed after 3 weeks of prolonged-release melatonin treatment. Sleep efficiency, wake time after sleep onset, and number of awakenings improved significantly with prolonged-release melatonin as compared with placebo. Following 5 months of prolonged-release melatonin treatment, mean HbA1c (\pm standard deviation) was significantly lower than at baseline ($9.13\% \pm 1.55\%$ versus $8.47\% \pm 1.67\%$, respectively, $P = 0.005$).

Conclusion: Short-term use of prolonged-release melatonin improves sleep maintenance in type 2 diabetic patients with insomnia without affecting glucose and lipid metabolism. Long-term prolonged-release melatonin administration has a beneficial effect on HbA1c, suggesting improved glycemic control.

Keywords: sleep, insulin, type 2 diabetes, glucose, melatonin

Introduction

Diabetes mellitus is a chronic age-related disease affecting an increasing number of patients worldwide and is currently reaching epidemic proportions.¹ Several studies have suggested a direct association between diabetes and sleep disturbances.^{2–7} Primary sleep disorders have been suggested to promote development of the metabolic syndrome that is strongly associated with increased type 2 diabetes and cardiovascular risk.⁷ On the other hand, uncontrolled diabetes may adversely affect sleep quality nonspecifically, as a result of night-time thirst, a sensation of dryness, and nocturia, symptoms of hypoglycemia (sweating and tachycardia), stress, anxiety, and depression. All of these factors may impair good sleep at night.

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Melatonin (N-acetyl-5-methoxytryptamine), the major hormone produced nocturnally by the pineal gland, is a sleep regulator and signal of darkness in humans. The circadian rhythm of synthesis and secretion of melatonin is closely associated with the sleep rhythm in both sighted and blind subjects.⁸ Daytime administration of exogenous melatonin (when it is not present endogenously) promotes sleep in humans⁸ and results in sleep-like brain activity patterns at specific areas such as the precuneus and hippocampus.^{9,10} Endogenous melatonin levels decrease with age,¹¹ and this decline may contribute to the common complaint of poor sleep quality in elderly people.¹² Abnormalities of the nocturnal melatonin profile have also been described in diabetic patients, mainly in those suffering from diabetic neuropathy.¹³ Post mortem studies have indicated an association between diabetes mellitus and decreased melatonin secretion.¹⁴ Melatonin deficiency deprives the brain of an important regulator of sleep and time cue to the internal circadian clock,¹⁵ and may thus exacerbate sleep problems in diabetic patients.

There is also a growing body of evidence suggesting a link between disturbance in melatonin production and impaired insulin, glucose, lipid metabolism, and antioxidant capacity.^{16–19} Furthermore, melatonin has been found to influence insulin secretion both in vivo and in vitro,¹⁸ and night-time melatonin levels are reportedly related to night-time insulin concentrations in patients with the metabolic syndrome.¹⁹ In several recent studies, a single nucleotide polymorphism of the human melatonin receptor 1B has been described as being causally linked to increased risk of developing type 2 diabetes.^{20–22} All these data suggest that endogenous as well as exogenous melatonin may play a role in improving diabetic control.

Melatonin has a very short half-life of 40–50 minutes,²³ and is quickly eliminated from the circulation, but physiological levels are maintained throughout the night as a result of continuous secretion by the pineal gland. Prolonged-release melatonin 2 mg is a new drug licensed to treat primary insomnia in patients aged 55 years and older. It exerts its effects by mimicking the release pattern of endogenous melatonin in the brain. In randomized, placebo-controlled clinical trials, prolonged-release melatonin 2 mg significantly improved sleep latency, quality of sleep, and morning alertness, as compared with placebo in patients aged 55 years and older,^{24–27} and improved sleep maintenance assessed by actigraphy.²⁸

The aim of the current study was to investigate the effect of prolonged-release melatonin 2 mg administered

at 9–11 pm for 3 weeks on glucose and lipid metabolism in community-dwelling diabetics suffering from insomnia. The effects of this treatment on sleep parameters were assessed in a subgroup of the patients using actigraphy. An extended period of 5 months of open-label, prolonged-release melatonin administration followed to evaluate the effects of prolonged-release melatonin on glycosylated hemoglobin (HbA1c) levels over a longer period of treatment, as an indicator of diabetic control.²⁹

Methods

The study was performed in accordance with the World Medical Assembly guidelines, ie, the latest version of the Declaration of Helsinki, and the standard operating procedures of Neurim Pharmaceuticals Ltd. All patients were given full details of the study in both verbal and written form by the investigator. Each patient gave their written informed consent for study participation according to Good Clinical Practice rules. The study protocol was approved by the Ethics Committee of the E Wolfson Medical Center, Holon, Israel.

Study design

In a randomized, double-blind, crossover design, the subjects were given tablets of either prolonged-release melatonin 2 mg (Circadin®, Rad Neurim Pharmaceuticals EEC Ltd) or an identical-looking placebo. The tablets were taken 2 hours before bedtime for a period of 3 weeks (period 1). This was followed by a washout period of 1 week and then by another 3-week period of treatment with the alternative preparation (period 2). Patients, investigators, and coworkers were blinded to the drug given during the crossover, double-blind treatment periods. Access to the randomization code was given to the pharmacist who prepared the tablets in containers. During the extension period of 5 months (period 3) prolonged-release melatonin was given nightly to all patients in an open-label manner. Treatment codes were opened after study completion and final entry of all study data.

Participants

Eligible patients were men and women diagnosed and treated for type 2 diabetes who also complained of insomnia. Patients with liver or renal disease (serum creatinine ≥ 1.5 mg/dL) were excluded. All concomitant medications were continued during the trial, and included metformin, sulfonylureas, glucosidase inhibitors, glitazones, insulin, statins, fibrates, angiotensin-converting enzyme inhibitors, calcium channel blockers, alpha-blockers, beta-blockers, antiplatelet agents,

antiarrhythmic drugs, nitrates, phosphodiesterase inhibitors, bronchodilators, and antidepressants.

Evaluation of sleep parameters

A subset of patients in the study were assigned (based on availability of equipment) to undergo recording of their activity-rest patterns by wrist actigraphy (Somnitor™, Neurim Pharmaceuticals Ltd, Tel Aviv, Israel³⁰) while sleeping at home. Motion recordings were analyzed as previously described²⁴ to evaluate total sleep time (time spent asleep after sleep onset), sleep efficiency (total sleep time divided by time in bed multiplied by 100%), wake after sleep onset (sum of mid sleep arousal times after sleep onset), number of awakenings (between sleep onset and offset), and sleep latency (the lag period between entering bed and sleep onset). Changes in each parameter averaged over 3 consecutive nights from the placebo run-in period (baseline) to the end of 3 weeks of treatment were calculated for each patient.

Laboratory assessment

Fasting blood was withdrawn from all patients for routine hematologic and biochemistry evaluation on the morning before randomization, the morning following the last night of treatment periods 1 and 2, and the morning following the end of period 3. These tests included complete blood count, serum urea, creatinine, sodium, potassium, chloride, calcium, phosphate, total protein, albumin, globulin, bilirubin, alkaline phosphatase, glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, lactic dehydrogenase, and creatine phosphokinase. In the double-blind periods, glycemic control and lipid metabolism were evaluated by assessment of fasting glucose, fructosamine, HbA1c, insulin (for patients not treated with insulin), C-peptide, triglycerides, and cholesterol (total, high-density and low-density lipoprotein). Several antioxidants were also assessed in plasma, ie, malone dialdehyde, conjugated dienes, catalase, and glutathione peroxidase and reductase. The patients were then given a standard meal and postprandial blood sampling for serum glucose, insulin, and C-peptide was performed two hours later. Laboratory testing of HbA1c and postprandial glucose was performed again following 5 months of prolonged-release melatonin treatment.

Statistical analysis

The data collected were analyzed using SAS version 6.10 (SAS, Cary, NC). The effects of prolonged-release melatonin on each of the laboratory parameters were compared using

a 2×2 mixed design analysis of covariance. The within-subject factor used was treatment (placebo versus prolonged-release melatonin) while the between-subject factor was order of administration (placebo then prolonged-release melatonin versus prolonged-release melatonin then placebo). The covariate used was the measure of the respective parameter at baseline (prestudy). The effect of prolonged-release melatonin on sleep parameters was evaluated using a 2×2 mixed design analysis of variance for repeated measurement. In addition, the interaction between the effects of prolonged-release melatonin and disease was assessed by analyses of covariance where the between-subject factor was insulin treatment for type 2 diabetes.

Results

A total of 36 independently living type 2 diabetic patients (16 on oral hypoglycemic agents and 20 on insulin) who also complained of insomnia were entered into the study. Eleven were men and 25 were women, and mean age \pm standard deviation was 63 ± 8 (range 46–77) years. All 36 patients completed the randomized crossover and extension parts of the study. Sleep quality was recorded by wrist actigraphy in a subgroup of 22 patients (seven men and 15 women). Statistical analyses of the efficacy of prolonged-release melatonin on sleep were therefore performed only in these 22 diabetic patients. One or both HbA1c measures were lacking in seven patients. Thus, statistical analyses of the long-term effects of prolonged-release melatonin on HbA1c were based on results obtained from 29 diabetic patients (10 men, 19 women), of whom 12 were treated with oral hypoglycemic agents and 17 were on insulin (see Figure 1 for full details).

A significant effect of order of administration ($F_{(1,24)} = 6.88$, $P < 0.05$) and a significant interaction between treatment and order of administration ($F_{(1,23)} = 5.44$, $P < 0.05$) were observed for fasting glucose; the mean serum glucose level on prolonged-release melatonin in the second crossover period was significantly lower than that during the first crossover period. No significant treatment effect on fasting glucose was found compared with placebo. No other significant treatment order effects in the laboratory parameters were found, nor any significant interactions between treatment and order.

The overall safety and tolerability results as well as diabetes status were similar in all treatment periods. Prolonged-release melatonin 2 mg had no significant effect on routine laboratory tests, glucose and lipid metabolism, or antioxidant levels. However, there was a significant decrease in HbA1c concentration from $9.13\% \pm 1.55\%$ at baseline to $8.47\% \pm 1.67\%$

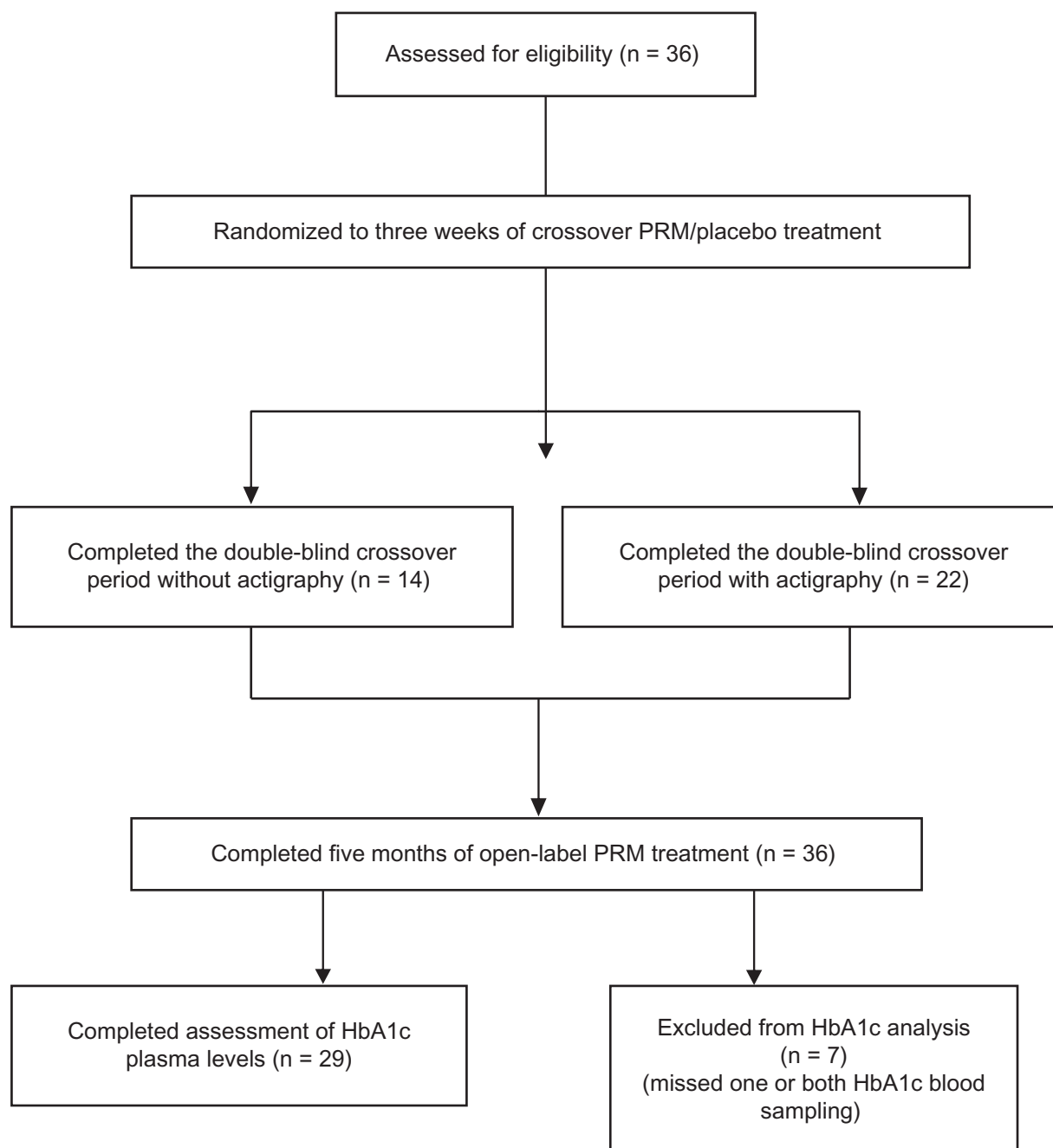


Figure 1 Overall patient disposition. Analysis of the short-term period included eligible patients who completed three weeks of double-blind treatment with prolonged-release melatonin or placebo. Analysis of the long-term period included patients treated open-label with prolonged-release melatonin for 5 months. Analyses of actigraphic motion recordings included eligible patients who completed 3 weeks of treatment with prolonged-release melatonin and placebo and provided actigraphy data by the end of the treatment period.

Abbreviation: PRM, prolonged-release melatonin.

following the five-month extension period ($t_{(29)} = 3.29$, $P = 0.005$, t -test for dependent samples). Of the 29 patients in whom HbA1c data on both time points were available, HbA1c levels decreased by 1% or more in 11 and increased in 1; the mean decrease in HbA1c was $0.66\% \pm 1.15\%$ regardless of the order of treatment in the randomization phase. A t -test for independent samples performed on the reduction in HbA1c

from prestudy levels to those after 5 months on prolonged-release melatonin, indicated that the reduction in HbA1c was not significantly different in type 2 diabetics treated or not treated by insulin ($P = 0.68$).

The effects of 3 weeks of prolonged-release melatonin compared with placebo on sleep parameters are depicted in Table 1. Statistically significant improvements in several

Table 1 Actigraphy-derived sleep parameters (mean \pm standard deviation) following 3 weeks of administration of prolonged-release melatonin or placebo (crossover, $n = 22$)

Parameter	Placebo	PRM	Order effect P value	Treatment by order P value	Treatment effect P value
Sleep efficiency (%)	79.2 \pm 9.8	83.0 \pm 11.7	0.86	0.31	<0.04
Sleep latency (minutes)	18.1 \pm 13.2	20.7 \pm 18.0	0.66	0.90	0.36
Wake after sleep onset (minutes)	66.3 \pm 38.7	38.0 \pm 22.1	0.58	0.85	<0.001
Total sleep time (minutes)	366.1 \pm 66.2	355.1 \pm 74.5	0.84	0.09	0.41
Number of awakenings	16.5 \pm 8.5	10.8 \pm 5.4	0.28	0.35	<0.003

Abbreviation: PRM, prolonged-release melatonin.

sleep parameters were found for prolonged-release melatonin compared with placebo (Table 1). Of the 22 patients in whom sleep assessments were performed, 12 had a net improvement of more than 3% in sleep efficiency on prolonged-release melatonin as compared with placebo, and 15 had a net improvement of at least 25% in wake after sleep onset. In 12 patients, the number of awakenings was improved by at least 25%, while only seven showed little or no improvement in any of the sleep parameters on prolonged-release melatonin compared with placebo. No significant treatment order effects or interactions between treatment and order were found in the sleep parameters.

Improvement in sleep parameters in the double-blind period did not predict change in HbA1c during the long-term period, and improvement in HbA1c levels was found both in patients in whom sleep quality was or was not improved.

No serious adverse events were reported. An adverse experience was reported seven times on prolonged-release melatonin treatment, ie, insomnia ($n = 2$), abnormal thoughts ($n = 1$), taste aversion ($n = 1$), and sexual dysfunction ($n = 3$), and five times on placebo treatment, ie, somnolence ($n = 3$), libido increase ($n = 2$), and sexual dysfunction ($n = 1$).

Discussion

These results show that prolonged-release melatonin is safe in diabetic patients, having no adverse effects on glucose and lipid metabolism or other routine biochemical tests, and no other adverse events during short-term (3 weeks) and long-term use. No interaction with any of the medications frequently used in diabetic patients was observed (ie, metformin, sulfonylureas, thiazolidinediones, peroxisome-proliferator activated receptors agonists, insulin, fibrates and other lipid-lowering agents, angiotensin-converting inhibitors, calcium antagonists, beta-blockers, anticoagulants, and serotonin reuptake inhibitors). Importantly, prolonged-release melatonin did not affect C-peptide levels, suggesting that it had no effect on the release of insulin in these patients.

It was shown that glucose tolerance and insulin sensitivity were both reduced as compared with placebo following a single oral administration of melatonin 1 mg in 22 postmenopausal nondiabetic women. The authors suggested that melatonin should be avoided in diabetes.³¹ Our findings do not support this notion, and indicate that prolonged-release melatonin does not impair insulin action or glucose tolerance in diabetic patients, whether used in the short term or long term. On the contrary, we have shown improved glycemic control upon long-term use of prolonged-release melatonin.

In two other studies, the combination of melatonin and zinc acetate alone or in combination with metformin was found to improve fasting and postprandial glycemic control in type 2 diabetic patients.³² Melatonin was not given alone in these studies, and it is therefore impossible to evaluate its specific effect on glycemic control. However, these results are in line with our data and support our findings regarding the safety of melatonin in diabetic patients.

Our findings of improved diabetic control with prolonged-release melatonin are also compatible with those of some animal studies. Long-term administration of time-release melatonin pellets (1.1 mg/day for 30 weeks) reduced the development of hypertriglyceridemia, hyperinsulinemia, and hyperleptinemia, and restored normal ratios of 20:3n–6/20:4n–6 phospholipids in a rat model of diabetes.³³ This finding suggests that long-term melatonin administration may slow down age-related deterioration in glucose and lipid metabolism. The decrease in HbA1c may be due to better compliance with diet and treatment as a result of participation in the study. Alternatively, it may be the result of an antistress effect of melatonin causing attenuation of glucose fluctuations.

Prolonged-release melatonin improved sleep maintenance in comparison with placebo, as indicated by improvements in sleep efficiency, wake after sleep onset, and number of awakenings. The effects were consistent with those seen in

placebo-controlled studies of prolonged-release melatonin in patients suffering from insomnia.^{24–28} Sleep latency did not improve on prolonged-release melatonin as compared with placebo, perhaps because the mean sleep latency in this population (18.1 ± 13.2 minutes) was only slightly longer than 15 minutes (a value considered normal). We did not find any significant differences in glucose or lipid metabolism during the 3 weeks of treatment with prolonged-release melatonin. Therefore, the effect on sleep maintenance is probably directly linked to the specific sleep-promoting effects of melatonin rather than improvement in diabetes control. Because the improvement in sleep in diabetic patients was not predictive of reduction in HbA1c, the effect of prolonged-release melatonin on HbA1c is probably not related to the improvement in sleep, but rather reflects a mechanism that involves glucose metabolism per se. Of 13 patients who responded to prolonged-release melatonin with an increase in sleep efficiency of 3% or more, seven were concomitantly on metformin, five on sulfonylureas, five on both metformin and sulfonylureas, one on pioglitazone, and seven were on insulin. Hence, the soporific activity of prolonged-release melatonin is probably independent of concomitant antidiabetic drug effects.

Melatonin may act at the level of the circadian clock in the suprachiasmatic nuclei of the hypothalamus to improve the robustness of the circadian system.¹⁵ An increase in endogenous glucose production is a major contributor to fasting morning hyperglycemia in type 2 diabetes. Endogenous glucose production and gluconeogenesis display diurnal rhythms that drive fasting hyperglycemia and are absent in healthy control subjects.³⁴ Melatonin is closely related to endogenous glucose production, but its secretion is attenuated in diabetes.³⁴ Diurnal variations in endogenous glucose production in diabetes may be related to reduction in the robustness of the suprachiasmatic nuclei in the hypothalamus in diabetes that may be responsible, at least in part, for low melatonin production in these patients. Timing and dose-controlled exogenous hormone supplementation aimed at normalizing melatonin levels have been shown to affect the circadian pacemaker by modifying the internal clock in humans.⁸ Melatonin treatment may thus reinforce circadian control of glucose metabolism and subsequently stabilize endogenous glucose production, reduce serum glucose, and eventually contribute to better glycemic control.

Long-term administration of low-dose, prolonged-release melatonin 2 mg/day was associated with a significant reduction in HbA1c in type 2 diabetic patients. Because a 0.5% HbA1c difference between successive results is considered

a clinically relevant change, our finding of a mean decrease of $0.66\% \pm 1.15\%$ in HbA1c is both statistically significant and of clinical importance.³⁵ It has been reported that each 1% reduction in HbA1c is associated with a risk reduction of 21% for any end point related to diabetes, suggesting that even a modest reduction in glycemia has the potential to prevent deaths from complications related to diabetes.³⁶ In the current study, more than one third of patients showed decreased HbA1c levels of 1% or more. Although no parallel placebo treatment was used during this period, this observation may suggest some antihyperglycemic activity for melatonin in humans.

Two major limitations of our study are that the long-term treatment was not placebo-controlled and the circadian rhythm of glucose production was not measured. Further studies to clarify the involvement of circadian modulation in improvement of diabetic control by prolonged-release melatonin, and the long-term nature of these effects, are warranted.

Disclosure

The study was an investigator-initiated trial and was funded by Neurim Pharmaceuticals Ltd. DG, MZ, and JW were the investigators and have no financial involvement with the company. ZM performed the laboratory assessments and has no financial connections with Neurim Pharmaceuticals Ltd. ML and NZ are employees of Neurim Pharmaceuticals Ltd.

References

1. Narayan KM, Gregg EW, Fagot-Campagna A, Engelgau MM, Vinicor F. Diabetes: a common, growing, serious, costly, and potentially preventable public health problem. *Diabetes Res Clin Pract.* 2000;50(Suppl 2): S77–S84.
2. Foley DJ, Monjan A, Simonsick EM, Wallace RB, Blazer DG. Incidence and remission of insomnia among elderly adults: an epidemiologic study of 6,800 persons over three years. *Sleep.* 1999;22(Suppl 2): S366–S372.
3. Chasens ER. Understanding sleep in persons with diabetes. *Diabetes Educ.* 2007;33(3):435–436.
4. Gottlieb DJ, Punjabi NM, Newman AB, et al. Association of sleep time with diabetes mellitus and impaired glucose tolerance. *Arch Intern Med.* 2005;165(8):863–867.
5. Barone MT, Menna-Barreto L. Diabetes and sleep: a complex cause-and-effect relationship. *Diabetes Res Clin Pract.* 2011;91(2):129–137.
6. Knutson KL, Van Cauter E, Zee P, Liu K, Lauderdale DS. Cross-sectional associations between measures of sleep and markers of glucose metabolism among subjects with and without diabetes: the Coronary Artery Risk Development in Young Adults (CARDIA) Sleep Study. *Diabetes Care.* 2011;34(5):1171–1176.
7. Eriksson AK, Ekblom A, Granath F, Hilding A, Efendic S, Ostenson CG. Psychological distress and risk of pre-diabetes and type 2 diabetes in a prospective study of Swedish middle-aged men and women. *Diabet Med.* 2008;25(7):834–842.
8. Cajochen C, Krauchi K, Wirz-Justice A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J Neuroendocrinol.* 2003;15(4):432–437.

9. Gorfine T, Assaf Y, Goshen-Gottstein Y, Yeshurun Y, Zisapel N. Sleep-anticipating effects of melatonin in the human brain. *Neuroimage*. 2006;31(1):410–418.
10. Gorfine T, Zisapel N. Late evening brain activation patterns and their relation to the internal biological time, melatonin, and homeostatic sleep debt. *Hum Brain Mapp*. 2009;30(2):541–552.
11. Sharma M, Palacios-Bois J, Schwartz G, et al. Circadian rhythms of melatonin and cortisol in aging. *Biol Psychiatry*. 1989;25(3):305–319.
12. Leger D, Laudon M, Zisapel N. Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. *Am J Med*. 2004;116(2):91–95.
13. O'Brien IA, Lewin IG, O'Hare JP, Arendt J, Corral RJ. Abnormal circadian rhythm of melatonin in diabetic autonomic neuropathy. *Clin Endocrinol (Oxf)*. 1986;24(4):359–364.
14. Sandyk R, Anastasiadis PG, Anninos PA, Tsagas N. Is the pineal gland involved in the pathogenesis of endometrial carcinoma. *Int J Neurosci*. 1992;62(1–2):89–96.
15. Zisapel N. Sleep and sleep disturbances: biological basis and clinical implications. *Cell Mol Life Sci*. 2007;64(10):1174–1186.
16. Nishida S. Metabolic effects of melatonin on oxidative stress and diabetes mellitus. *Endocrine*. 2005;27(2):131–136.
17. Korkmaz A, Reiter RJ, Topal T, Manchester LC, Oter S, Tan DX. Melatonin: an established antioxidant worthy of use in clinical trials. *Mol Med*. 2009;15(1–2):43–50.
18. Peschke E. Melatonin, endocrine pancreas and diabetes. *J Pineal Res*. 2008;44(1):26–40.
19. Robeva R, Kirilov G, Tomova A, Kumanov P. Melatonin-insulin interactions in patients with metabolic syndrome. *J Pineal Res*. 2008;44(1):52–56.
20. Prokopenko I, Langenberg C, Florez JC, et al. Variants in MTNR1B influence fasting glucose levels. *Nat Genet*. 2009;41(1):77–81.
21. Tam CH, Ho JS, Wang Y, et al. Common polymorphisms in MTNR1B, G6PC2 and GCK are associated with increased fasting plasma glucose and impaired beta-cell function in Chinese subjects. *PLoS One*. 2010;5(7):e11428.
22. Mussig K, Staiger H, Machicao F, Haring HU, Fritsche A. Genetic variants in MTNR1B affecting insulin secretion. *Ann Med*. 2010;42(6):387–393.
23. Waldhauser F, Waldhauser M, Lieberman HR, Deng MH, Lynch HJ, Wurtman RJ. Bioavailability of oral melatonin in humans. *Neuroendocrinology*. 1984;39(4):307–313.
24. Wade A, Downie S. Prolonged-release melatonin for the treatment of insomnia in patients over 55 years. *Expert Opin Investig Drugs*. 2008;17(10):1567–1572.
25. Luthringer R, Muzet M, Zisapel N, Staner L. The effect of prolonged-release melatonin on sleep measures and psychomotor performance in elderly patients with insomnia. *Int Clin Psychopharmacol*. 2009;24(5):239–249.
26. Wade AG, Ford I, Crawford G, et al. Nightly treatment of primary insomnia with prolonged release melatonin for 6 months: a randomized placebo controlled trial on age and endogenous melatonin as predictors of efficacy and safety. *BMC Med*. 2010;8:51.
27. Wade AG, Crawford G, Ford I, et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. *Curr Med Res Opin*. 2011;27(1):87–98.
28. Garfinkel D, Laudon M, Nof D, Zisapel N. Improvement of sleep quality in elderly people by controlled-release melatonin. *Lancet*. 1995;346(8974):541–544.
29. Coniff RF, Shapiro JA, Robbins D, et al. Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM. A placebo-controlled dose-comparison study. *Diabetes Care*. 1995;18(6):817–824.
30. Wrist activity based monitoring of nocturnal sleep: validation of a novel scoring algorithm. Ninth annual meeting of the Associated Professional Sleep Societies, Nashville, TE; 1995.
31. Cagnacci A, Arangino S, Renzi A, et al. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. *Clin Endocrinol (Oxf)*. 2001;54(3):339–346.
32. Hussain SA, Khadim HM, Khalaf BH, Ismail SH, Hussein KI, Sahib AS. Effects of melatonin and zinc on glycemic control in type 2 diabetic patients poorly controlled with metformin. *Saudi Med J*. 2006;27(10):1483–1488.
33. Nishida S, Segawa T, Murai I, Nakagawa S. Long-term melatonin administration reduces hyperinsulinemia and improves the altered fatty-acid compositions in type 2 diabetic rats via the restoration of delta-5 desaturase activity. *J Pineal Res*. 2002;32(1):26–33.
34. Radziuk J, Pye S. Diurnal rhythm in endogenous glucose production is a major contributor to fasting hyperglycaemia in type 2 diabetes. Suprachiasmatic deficit or limit cycle behaviour? *Diabetologia*. 2006;49(7):1619–1628.
35. Lenters-Westra E, Slingerland RJ. Hemoglobin A1c point-of-care assays; a new world with a lot of consequences! *J Diabetes Sci Technol*. 2009;3(3):418–423.
36. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–412.

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