Effects of melatonin supplementation in patients with type 2 diabetes mellitus and chronic periodontitis under nonsurgical periodontal therapy: A double-blind randomized controlled trial

Hadi Bazyar1,2, Ahmad Zare Javid3,4, Mehrnoosh Zakerkish1, Hojat Allah Yousefimanesh5, Mohammad Hosein Haghighi-Zadeh6

1Health Research Institute, Diabetes Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, 2Student Research Committee, Ahvaz Jundishapur University of Medical Science, Ahvaz, Iran, 3Nutrition and Metabolic Diseases Research Center, Clinical Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, 4Department of Nutrition, School of Allied Medical Sciences, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, 5Department of Periodontology, School of Dentistry, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, 6Department of Biostatistics, School of Public Health, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

Background: The aim of the present study was to investigate the effects of melatonin supplementation along with nonsurgical periodontal therapy (NSPT) in patients with type 2 diabetes mellitus (T2DM) and chronic periodontitis (CP).

Materials and Methods: The present study was a double-blind clinical trial. Fifty diabetic patients with periodontitis were randomly allocated to control (n = 25) and intervention groups (n = 25). Two tablets of 250 mg melatonin (6 mg net melatonin) or placebo were received by the intervention or control groups once a day for 8 weeks. Fasting blood glucose (FBG), glycosylated hemoglobin levels (HbA1c), lipid profile, systolic and diastolic blood pressure (SBP and DBP), anthropometric indices including weight, waist and hip circumference (WC and HC), and body mass index (BMI) were measured in patients at the beginning and end of the intervention.

Results: Forty-four patients (22 patients in each group) completed the study. In the intervention group, a significant reduction was observed in HbA1c (P = 0.004), weight, BMI, WC, HC (all P < 0.001), DBP (P = 0.017), and SBP (P = 0.006). The high-density lipoprotein-cholesterol was significantly increased in the intervention group after the intervention (P = 0.007). Moreover, after the adjustment of confounding factors, the mean changes of HbA1c (mean difference: −1.30, confidence interval [CI]: −2.41–−0.19, P = 0.02), weight (mean difference: −3.90, CI: −5.30–−2.50, P < 0.001), WC (mean difference: −1.37, CI: −2.19–−0.55, P = 0.002), BMI (mean difference: −1.41, CI: −1.92–−0.89, P < 0.001), HC (mean difference: −3.55, CI: −4.74–−2.35, P < 0.001), and SBP (mean difference: −1.24, CI: −2.41–−0.06, P = 0.03) improved significantly in the intervention group by comparison with the control group. No side effects were reported during the study.

Conclusion: The adjunct therapy of NSPT and melatonin may be useful in controlling the glycemic index, lipid profile, BP, and weight in T2DM with CP.

Key words: Blood glucose, melatonin, obesity, periodontal disease, serum lipids, type 2 diabetes mellitus

How to cite this article: Bazyar H, Zare Javid A, Zakerkish M, Yousefimanesh HA, Haghighi-Zadeh MH. Effects of melatonin supplementation in patients with type 2 diabetes mellitus and chronic periodontitis under nonsurgical periodontal therapy: A double-blind randomized controlled trial. J Res Med Sci 2022;27:52.
INTRODUCTION

Diabetes mellitus (DM) is a disturbance of metabolism recognized by high blood glucose. The cause is insulin resistance or insufficient insulin secretion or both.\(^1\) According to the International Diabetes Federation in 2017, it was estimated that 425 million adults suffer from diabetes, with more than 90% having type 2 DM (T2DM).\(^2\) Chronic and permanent hyperglycemia is associated with serious complications affecting all organs of the body including the gingival and periodontal tissues.\(^3\)

Periodontal disease is characterized by chronic inflammatory disorder along with infection leading to the progressive degradation of connective tissue attachment, the destruction of the supporting tissues of the teeth, and bone resorption.\(^4\) The prevalence of periodontal disease is about three times higher in diabetic patients compared with healthy individuals.\(^5\) Several evidences indicate a bidirectional relationship between DM and periodontal diseases. DM may considerably influence the periodontium, and on the other hand, evidence suggests that periodontal disease may adversely affect glycemic status in DM.\(^6\) It has been shown that periodontitis is related to important increase in the levels of glycosylated hemoglobin (HbA1c) and fasting blood glucose (FBG) in diabetic patients.\(^7\) It is also suggested that oxidative stress has a critical role in the pathogenesis of periodontal disease and diabetes.\(^8\) As oxidative stress has harmful effects on the development of T2DM and progression of its macro- and microvascular complications, antioxidant therapy has been suggested as a supplementary helpful approach in controlling T2DM.\(^9\)

Melatonin or N-acetyl-5-methoxytryptamine as an endogenous anti-inflammatory and antioxidant protein is produced primarily via the pineal gland.\(^10\) This hormone is derived from tryptophan and secreted during the night and regulates circadian rhythm and seasonal changes.\(^11\) Melatonin is a natural antioxidant and can eliminate free radicals.\(^12\) There are numerous reports indicating that serum levels of melatonin are increased in animals after eating foods rich in melatonin (such as cherry, walnuts, and strawberry).\(^13\) It has been shown that daily intake of melatonin decreased plasma leptin and adiponectin, body weight, cholesterol, triglycerides (TGs), glucose levels, and insulin.\(^14\) Therefore, it is suggested that melatonin may have anti-obesity, antihypertensive, and hypolipidemic effects.\(^15\) Hence, it is assumed that nonsurgical periodontal therapy (NSPT) along with melatonin supplementation may play a two-way role to control diabetes and periodontal disease against the lack of effect (hypothesis). According to our best knowledge, no study has been performed to investigate the effects of melatonin along with NSPT in T2DM with chronic periodontitis (CP). Therefore, the purpose of the present study was to evaluate the effects of melatonin supplementation in diabetic patients with CP under NSPT.

MATERIALS AND METHODS

Subjects and study design
This double-blind randomized clinical trial with parallel intervention and single center was done in the outpatient clinic of endocrinology and metabolism of Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Iran, from March 2017 to August 2017. In the present study, 96 T2DM patients with periodontal disease were enrolled. For further diagnosis and confirmation of periodontal disease, patients were referred to the dental clinic. Forty-six people were excluded from the study (12 disapproval to participate in the research and 34 did not have inclusion criteria). According to the inclusion criteria, fifty patients were randomly allocated to the intervention group (n = 25) or the control group (n = 25) [Figure 1]. The block design was used for randomization. In this method, all patients were divided into 6 groups with 4 blocks and two codes A and B were used according to the pattern (AABB, BBAA, ABAB, BABA, ABBA, and BABA). To distribute all patients (50 patients) in two groups, this pattern was repeated and the last two patients received A and B codes. The randomization method was double-blinded (the investigator and patients did not inform of the randomization of patients in two intervention or placebo groups). The coding program was performed by an out-of-study person who was related to the health-care system and did not know the type of intervention.

Inclusion and exclusion criteria
Diabetic patients with a history of more than 5 years from the time of diagnosis in both genders (male and female), 30–60 years old, body mass index (BMI) range between 18.5 and 30 kg/m\(^2\), confirmed DM (more than 5 years since diagnosis), and patients with severity of mild-to-moderate periodontitis (clinical attachment level (CAL) = 1–4 mm and pocket depth (PD) ≥ 4 mm) were the inclusion criteria. Furthermore, patients with the following conditions were excluded from the study: kidney failure, thyroid disease, other serious systemic diseases, pregnant and lactating women, hospitalized due to diabetes complications, hemoglobinopathies, anemia, uremia hemodialysis, traveling more than 2 weeks during the study, smoking, individuals with severe periodontitis, use of immunosuppressive medications, insulin injections, important changes in diabetes medications, history of NSPT during the past 6 months, consumption of antibiotics and any antioxidants and anti-inflammatory agents, the consumption of <90% of prescribed tablets, and significant dietary changes in the last 6 months. According to the guideline, patients who had
HbA1c ≥6.5%, FBG ≥126 mg/dl, or 2-hour glucose) 2 hpp (≥ 200 mg/dl were recognized as T2DM.[19]

Ethical considerations
The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved the present research project (IR. AJUMS.REC.1395.685). This work was approved by the website of the Iranian Registry of Clinical Trials (registration number: IRCT2017011631993N1).

Intervention protocol
The control group used two tablets of placebo (250 mg/day, 1 h before bedtime; provided by the school of Pharmacy at Ahvaz Jundishapur University of Medical Sciences) containing magnesium stearate, cellulose, silicon dioxide, and starch. Furthermore, the intervention group used two tablets of melatonin (250 mg/day, 1 h before bedtime) containing 3 mg net melatonin, sodium starch glycolate, and magnesium stearate for 8 weeks. The melatonin and placebo tablets were similar in terms of color, shape, taste, and size. To flavor placebo tablets, a few drops of peppermint oil were added to tablets. All patients were checked for possible side effects of melatonin three times during the intervention. The compliance of patients was evaluated by counting the remaining tablets. Patients with the use of <90% of prescribed tablets were excluded from the work. Patients were advised to continue their usual physical activities and follow any prescribed diabetic diet during the study. In this study, all subjects received routine diabetes therapy (using insulin was exclusion criteria).

Assessment of anthropometric and periodontal indices, blood pressure, nutritional intake, and physical activity
Anthropometric indices include weight, BMI, height, waist circumference (WC), hip circumference (HC), and waist-to-hip ratio. A nutritionist measured all the indices. Weight and height were measured by a digital scale. BMI was obtained using dividing the weight (kilograms) by height (meter square). After 20 min of rest, blood pressure measurement was done in the morning. The Nutritionist 4 software was used for the analysis of dietary intake (the results were already reported).[17] At the beginning of the study, along with melatonin supplementation, both the groups received NSPT. The NSPT included scaling and root surface debridement which is a careful cleaning of the root surfaces to clean calculus (tartar) and plaque from deep periodontal pockets and to smooth the tooth root to eliminate bacterial toxins. Furthermore, some oral health trainings (how to brush correctly and using of dental floss) were provided. Patients were not allowed to use mouthwash. The method of measuring periodontal indices is presented in our previous article.[17] The International Physical Activity Questionnaire was used to calculate physical activity. As, 0–600 min/week was considered light activity, 600–3000 min as moderate activity, and over 3000 min as heavy activity.[19]

Biochemical assays
After overnight fasting of 12 h, 5 ml of venous blood sample was collected at the beginning and end of the study. Some blood sample was isolated from each patient to measure HbA1c. Furthermore, serum levels of FBG, high-density lipoprotein (HD), low-density lipoprotein (LDL), TG, and cholesterol (CHOL) were measured. The enzymatic method was used to measure HbA1c (using Pars Azmoon kits, Tehran, Iran). Furthermore, the enzymatic method was used to measure HDL (using Nycocard kits, Norway). The colorimetric method (using Pars Azmoon kits, Tehran, Iran) was also used for the measurement of TG, CHOL, and HDL. The Friedewald formula was used for the calculation of LDL and VLDL.[19]

LDL-c (mg/dL) = TC (mg/dL) − HDL-c (mg/dL) − TG (mg/dL)/5.

Statistical analysis
The data were analyzed by SPSS 23 (IBM SPSS Statistics, Armonk, USA). The normality of the data was assessed using the Kolmogorov-Smirnov test. All data were presented as mean values and standard deviation. Qualitative data comparison was performed using Chi-square test (sex and physical activity levels). The results were compared between the two groups with the Independent t-test. The paired sample t-test was also used to compare within-group differences (beginning and end of the intervention). At the end of the study, significant differences between the two groups were assessed by analysis of covariance (ANCOVA) after the adjustment of confounding factors (disease duration, age, job, physical activity, sex, education, drugs, and energy). In ANCOVA, the assumption of equal variances was checked using Levene’s test, and if P ≥ 0.05, it showed that the variances were equal. P < 0.05 was considered statistically significant. Based on Ramezanpour et al.’s study[20] and considering systolic blood pressure (SBP) (confidence interval [CI] of 95%, power of 80%, effect size = 6.7, and design effect = 1.2), the sample size was computed according to this formula:

$$n = \left( \frac{z_1 \cdot \frac{\alpha}{2} + z_1 \cdot \beta}{\delta_1^2 + \delta_2^2} \right) \left( \frac{\delta_1 + \delta_2}{\delta_1 - \delta_2} \right)^2$$

calculated as 21 patients in each group. Considering with 10% probable withdrawing, 25 patients were included for each group.

RESULTS
Normal distributions were observed for all data and the variances were equal. Forty-four patients (22 patients
per group) completed the research and 6 patients were excluded from the study (3 discontinued intervention and 3 never received supplement or placebo). At the start of the study, no significant difference was observed in age, duration of diabetes, demographic characteristics, physical activity, and medications (data not shown) between the two groups ($P \geq 0.05$) [Table 1]. No specific side effects were reported for 8 weeks. Food intake (micronutrients, macronutrients, and energy) was not significantly different between the intervention and control groups at the beginning and end of the study. The relevant results are reported in our previous study.[17]

Glycemic status
At the start of the study, there were no statistically significant differences between the intervention and control groups for FBG and HbA1 ($P \geq 0.05$). In the intervention group, there was a significant reduction in the mean serum levels of HbA1c (8.64% ± 1.66% vs. 7.67% ± 1.19%, respectively, $P = 0.004$). The intervention resulted in a significant reduction in the mean changes of HbA1c compared with the placebo group ($-0.97\% \pm 1.42\%$ vs. $-0.18\% \pm 0.72\%$, respectively; mean difference: $-0.78$, CI: $-1.48–-0.09$, $P = 0.02$). Furthermore, after the adjustment of confounding factors (age, sex, physical activity, body weight, BMI, WC, and HC, disease duration, energy, and drugs), the mean changes of HbA1c remained significant (mean difference: $-1.30$, CI: $-2.41–-0.19$, $P = 0.02$). Serum levels of FBG had a nonsignificant decrease in the intervention group ($P = 0.14$) [Table 2].

Lipid profile
Melatonin with NSPT significantly increased serum levels of HDL postintervention ($44.36 \pm 7.9$ mg/dl vs. $48.72 \pm 9.78$ mg/dl, respectively, $P = 0.007$). However, the intervention had no significant effects on improving serum levels of TG, CHOL, and LDL-cholesterol (LDL-C). Furthermore, in the intervention group, the mean changes of HDL were significantly higher compared with the control group after the intervention ($4.36 \pm 6.8$ mg/dl vs. $-0.81 \pm 6.26$ mg/dl, respectively; mean difference: 5.18, CI: 1.18–9.17, $P = 0.01$), but after removing the confounding factors (age, sex, energy, body weight, BMI, WC, and HC, physical activity, disease duration, and drugs), this was not significant (mean difference: 5.16, CI: $-2.01–12.34$, $P = 0.15$) [Table 2].

Blood pressure
Mean systolic and diastolic blood pressure (SBP and DBP) did not differ significantly between the two groups at the beginning of the study ($P \geq 0.05$). The mean levels of SBP and DBP were significantly decreased in the intervention group ($P = 0.006$ and $P = 0.017$, respectively) postintervention. The mean differences of SBP and DBP were significantly lower in the melatonin group compared with the placebo group after the treatment ($-1.00 \pm 1.54$ mmHg vs. $0.13 \pm 0.88$ mmHg, respectively; mean difference: $-1.13$, CI: $-1.90–0.37$, $P = 0.005$) and DBP ($-0.36 \pm 0.65$ mmHg vs. $0.13 \pm 0.77$ mmHg, respectively; mean difference: $-0.50$, CI: $-0.93–-0.06$, $P = 0.02$). Although the mean changes of SBP remained significant (mean difference: $-1.24$, CI: $-2.41–-0.06$, $P = 0.03$), it did not remain significant for DBP (mean difference: $-0.52$, CI: $-1.15–0.10$, $P = 0.10$) [Table 3].

Anthropometric indices
At baseline, there was no significant difference in body weight, BMI, WC, and HC between the two groups ($P \geq 0.05$). The mean body weight ($73.68 \pm 8.38$ kg vs. $70.31 \pm 8.09$ kg, respectively; $P < 0.001$), BMI ($27.21 \pm 2.19$ kg/m$^2$ vs. $25.98 \pm 2.24$ kg/m$^2$, respectively; $P < 0.001$), WC ($101.22 \pm 9.99$ cm vs. $99.68 \pm 10.18$ cm, respectively; $P < 0.001$), and HC ($106.59 \pm 9.7$ cm vs. $103.31 \pm 9.93$ cm, respectively; $P < 0.001$) were significantly reduced in the melatonin group postintervention. The mean changes of body weight, BMI, WC, and HC were significantly lower in the melatonin group compared with the placebo group postintervention ($-3.36 \pm 2.57$ kg vs. $0.22 \pm 1.65$ kg, respectively; mean difference: $-3.59$, CI: $-4.90–2.27$, $P < 0.001$), BMI ($-1.23 \pm 0.95$ kg/m$^2$ vs. $0.06 \pm 0.58$ kg/m$^2$, respectively; mean difference: $-1.30$, CI: $-1.78–-0.82$, $P < 0.001$), WC ($-1.54 \pm 1.50$ cm vs. $-0.18 \pm 0.95$ cm, respectively; mean difference: $-1.36$, CI: $-2.13–-0.59$, $P = 0.001$), and HC ($-3.27 \pm 2.33$ cm vs. $0.13 \pm 0.94$ cm, respectively; mean difference: $-3.40$, CI: $-4.50–-2.30$, $P < 0.001$). Furthermore, after the adjustment of confounding factors (age, sex, physical activity, energy, drugs, and disease duration), the mean changes of WC (mean difference: $-1.37$, CI: $-2.19–0.55$, $P = 0.002$), weight (mean difference: $-3.90$, CI: $-5.30–2.50$, $P < 0.001$),

---

Table 1: The characteristics of subjects at baseline

| Variable                      | Control group | Intervention group | $^pP$  |
|-------------------------------|---------------|--------------------|--------|
|                              | (n=22)        | (n=22)             |        |
| Gender (%)                    |               |                    |        |
| Female                        | 53.3          | 46.7               | 0.51*  |
| Age (years)                   | 51.45±5.03    | 53.72±6.68         | 0.21   |
| BMI (kg/m$^2$)                | 27.36±2.1     | 27.21±2.19         | 0.83   |
| Physical activity (met-min/week) | 320.86±171.7  | 293.31±175.79      | 0.60   |
| Levels of physical activity (n) |           |                    |        |
| Light                         | 19            | 20                 | 0.63a  |
| Moderate                      | 3             | 2                  |        |
| Heavy                         | 0             | 0                  |        |
| Disease duration (years)       | 7.36±2.87     | 7.77±2.59          | 0.71   |

$^pP<0.05$ was considered significant using independent t-test between the two groups at baseline, $^aP<0.05$ was considered significant using Chi-square test. Values are expressed as means±SD; SD=Standard deviation; BMI=Body mass index
BMI (mean difference: −1.41, CI: −1.92–−0.89, \(P < 0.001\)), and HC (mean difference: −3.55, CI: −4.74–−2.35, \(P < 0.001\)) remained significant [Table 3].

**DISCUSSION**

**Melatonin and glycemic control**

Based on the results of the present study, consumption of melatonin with NSPT had a significant reducing effect on HbA1c. Hence, it is suggested that melatonin with NSPT may improve glycemic status in T2DM. Few human studies have studied the effects of melatonin on...
glycemic control. Similar to the present study, Rezvanfar et al. showed that 3-month consumption of melatonin improved glycemic control.[21] In another clinical trial, 12-week administration of 10 mg melatonin significantly increased insulin sensitivity and decreased serum concentration of insulin, insulin resistance, and plasma FBG. Furthermore, a higher dose of melatonin in the same study resulted in a significant reduction in serum levels of FBG.[22] Concur with the finding of this study, Koziróg et al. presented that daily consumption of 5 mg melatonin for 2 months had no significant decrease in blood glucose in patients with metabolic syndrome.[23] Lower dosage and intervention period of melatonin at the present study may be considered possible reasons for having not significant reduction levels of FBG. According to several studies, high levels of insulin in diabetic patients may lead to an inhibitory effect on the pineal gland and secretion of melatonin from it, therefore, a functional antagonism is assumed between melatonin and insulin. These studies suggest that the pineal gland and its melatonin-synthesizing machinery are sensitive to any alteration in insulin levels. Several studies have found that higher insulin and glucose levels are associated with lower levels of melatonin in T2DM. On the other hand, it has been stated that melatonin increases glucose tolerance, insulin sensitivity, and the gene expression of glucose transporter type 4 in insulin-sensitive tissues (such as cardiac muscles, skeletal, white, and brown adipose tissue).[24]
Bazyar, et al.: Melatonin in patients with T2DM and CP

Melatonin and lipid profile
The present study showed that HDL was increased postintervention, but no significant changes were observed in levels of CHOL, TG, LDL-C, and VLDL. In agreement with this study, it was reported that after 3 months of melatonin consumption, the levels of HDL-cholesterol increased, but no significant changes were seen in TG, CHOL, and LDL.

In this study, selecting the patients without dyslipidemia (based on inclusion criteria) may be the reason behind not finding any useful effects of melatonin on lipid profile. The valuable impacts of melatonin on lipid profile were approved by several studies in diabetic patients.

Figure 1: Stages of clinical trial progress

Melatonin and blood pressure
The findings of this study indicated that melatonin consumption significantly declined SBP and DBP in T2DM with periodontal disease. There are few studies about the effects of melatonin on blood pressure. Similar to the findings of this study, Pakravan et al. found that consumption of melatonin significantly decreased SBP and DBP in patients with nonalcoholic fatty liver. Unlike this study, Simko et al. showed that melatonin did not affect SBP in rats. Different study subjects and dosage of melatonin may be considered some possible factors behind finding no significant effects. Some studies have shown the sympathetic effect of melatonin and interference in the renin-angiotensin system.
Melatonin and obesity

Several studies showed that melatonin is involved in the regulation of body fat mass and energy expenditure and effective control of weight gain and obesity. Few human studies investigated the effects of melatonin on weight and body composition in diabetic patients. After the melatonin supplementation, a significant decrease was observed in weight and WC. This result was in agreement with the present study. In addition, 8-week treatment with melatonin (4 mg/kg) in obese rats (induced by a high-fat diet) significantly reduced body weight and other metabolic markers. In contrast to this study, there was no significant improvement in body weight and BMI after 30-day consumption of melatonin in T2DM patients. Moreover, in another study, Mohammadi et al. showed that treatment with melatonin for 3 months had no significant changes in weight and BMI in individuals with overweight or obesity, but body fat percentage was significantly reduced in the melatonin group. The dosage of supplement, study duration, target community, illness severity, and clinical setting may be supposed for the diversity in the results. Recent studies on the cause of obesity have investigated the role of common single-nucleotide polymorphisms located in circadian system regulatory genes such as melatonin. The anti-obesogenic effect of melatonin may be due to its role in the regulation of energy expenditure by the activation of brown adipose tissue and influence energy balance mainly through regulating energy flow from different stores. Studies have shown that obesity induces low degree of systemic inflammation. Melatonin can decrease the production of inflammatory factors by inhibiting the phosphorylation of nuclear factor kappa-light-chain-enhancer of activated B-cells – the dependent cellular pathway that produces inflammatory mediators. Hence, melatonin can also reduce obesity in this way.

The absence of further study groups may be cited as a limitation of this work. It is suggested to do other research with four groups in future. Additionally, the small sample size based on study power and many exclusion criteria in the present study could limit the generalizability of the findings to a larger population. Hence, further studies with longer duration and two extra groups that a group used only placebo without NSPT and melatonin and an intervention group that received only melatonin supplement without NSPT, and a larger study with some form of stratification is required to confirm the helpful effects of NSPT along with melatonin supplementation in the management of diabetic patients with CP. Despite the mentioned limitations, this was the first study that investigated the impacts of oral supplementation of melatonin with NSPT in T2DM with CP. Furthermore, the adjustment for confounding factors gave more credit to the therapeutic effects of NSPT with melatonin.

CONCLUSION

Practical and clinical application

Our findings showed that 8-week melatonin supplementation in adjunct with NSPT may improve glycemic control, lipid profile, and blood pressure and would be beneficial in weight control in T2DM with CP. Therefore, the use of melatonin with NSPT can be beneficial as an adjunct therapy in the treatment of patients with T2DM and CP.

Acknowledgments

This study was funded by Vice-Chancellor for Research Affairs of Ahvaz Jundishapur University of Medical Sciences (NRC-9507 and Ref No. IR.AJUMS.REC.1395.685). The authors would like to thank the Dental Clinic of Ahvaz Jundishapur University of Medical Sciences, Nutrition and Metabolic Disorders Research Center, and Research Center for Diabetes, and Endocrinology and Metabolism clinic employees of Golestan Hospital. This work is resulted from the M.Sc thesis of MR Bazyar.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bazyar H, Adibmanesh A, Javid AZ, Maghsoumi-Norouzabad L, Gravand E, Alipour M, et al. The relationship between metabolic factors and anthropometric indices with periodontal status in type 2 diabetes mellitus patients with chronic periodontitis. Obes Med 2019;16:100138.
2. Cho NH, Shaw JE, Karuranga S, Huang Y, da Rocha Fernandes JD, Ohlrogge AW, et al. IDF diabetes atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271-81.
3. Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: Update on associations and risks. J Clin Periodontol 2008;35:398-409.
4. Ferreira MC, Dias-Pereira AC, Branco-de-Almeida LS, Martins CC, Paiva SM. Impact of periodontal disease on quality of life: A systematic review. J Periodontal Res 2017;52:651-65.
5. Emrich LJ, Shlossman M, Genco RJ. Periodontal disease in non-insulin-dependent diabetes mellitus. J Periodontol 1991;62:123-31.
6. Aryal S, Pradhana H, Shrestha SM. Does improved periodontal health affect metabolic and inflammatory markers in patients with diabetes mellitus? A comparative study. J Nep Soc Perio Oral Implantol 2017;1:6.
7. Mauri-Obradors E, Merlos A, Estrugo-Devesa A, Jané-Salas E, López-López J, Viñas M. Benefits of non-surgical periodontal treatment in patients with type 2 diabetes mellitus and chronic periodontitis: A randomized controlled trial. J Clin Periodontol 2018;45:345-53.
8. Javid AZ, Hormoznejad R, Allah Yousefimanes H, Zakerkish M, Haghighi MH, Ravanbakhsh M. GW27-e0215 the impact of resveratrol supplementation on blood glucose, insulin, insulin
resistance, triglyceride and periodontal markers in type 2 diabetic patients with chronic periodontitis. J Am Coll Cardiol 2016;68 Suppl 16:C183.

9. Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeeed M, et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: A randomized controlled trial. Inflammopharmacology 2017;25:25-31.

10. Jiang T, Chang Q, Cai J, Fan J, Zhang X, Xu G. Protective effects of melatonin on retinal inflammation and oxidative stress in experimental diabetic retinopathy. Oxid Med Cell Longev 2016;2016:3528274.

11. Stehle JH, Saade A, Rawashdeh O, Ackermann K, Jilg A, Sebestény T, et al. A survey of molecular details in the human pineal gland in the light of phylogeny, structure, function and chronobiological diseases. J Pineal Res 2011;51:17-43.

12. Tan DX, Manchester LC, Terron MP, Flores IJ, Reiter RJ. One molecule, many derivatives: A never-ending interaction of melatonin with reactive oxygen and nitrogen species? J Pineal Res 2007;42:28-42.

13. Reiter RJ, Manchester LC, Tan DX. Melatonin in walnuts: Influence on levels of melatonin and total antioxidant capacity of blood. Nutrition 2005;21:920-4.

14. Oanaolapo AY, Oanaolapo OJ. Circadian dysrhythmia-linked diabetes mellitus: Examining melatonin’s roles in prophylaxis and management. World J Diabetes 2018;9:99-114.

15. Rios-Lugo MJ, Cano P, Jimenez-Ortega V, Fernandez-Mateos MP, Scacchi PA, Cardinalli DP, et al. Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. J Pineal Res 2010;49:342-8.

16. Hosseini SA, Ghaedi E, Zakerkish M, Ghadiri A, Ashyary-larky D, Safari M, et al. Effects of ginseng extract on chemerin, apelin and glycemic biomarkers in type 2 diabetic patients. Indian J Physiol Pharmacol 2017;61:152-8.

17. Bazyar H, Gholinezhad H, Moradi L, Salehi P, Abadi F, Ravanbakhsh M, et al. The effects of melatonin supplementation in adjunct with non-surgical periodontal therapy on periodontal status, serum melatonin and inflammatory markers in type 2 diabetes mellitus patients with chronic periodontitis: A double-blind, placebo-controlled trial. Inflammopharmacology 2019;27:67-76.

18. Bazyar H, Ahmadi A, Zare Javid A, Irani D, Mohammadi Sartang M, Haghighazadeh MH. The association between dietary intakes and stone formation in patients with urinary stones in Shiraz. Med J Islam Repub Iran 2019;33:8.

19. Knopfholz J, Disserer CC, Pierin AJ, Schirr FL, Streisky L, Takito LL, et al. Validation of the friedewald formula in patients with metabolic syndrome. Cholesterol 2014;2014:261878.

20. Ramezanpour MR, Hosseini E, Naghibi S. The short-term effects of melatonin supplement consumption on some cardiac parameters of active young women before, during and after exhaustive activity. MJMS 2014;57:512-21.

21. Rezvanfar MR, Heshmati G, Chehrei A, Haghighi F, Rafiee F, Rezvanfar F. Effect of bedtime melatonin consumption on diabetes control and lipid profile. Int J Diabetes Dev Ctries 2017;37:74-7.

22. Raygan F, Ostadomohammadi V, Bahmani F, Reiter RJ, Asemi Z. Melatonin administration lowers biomarkers of oxidative stress and cardio-metabolic risk in type 2 diabetic patients with coronary heart disease: A randomized, double-blind, placebo-controlled trial. Clin Nutr 2019;38:391-6.

23. Koziróg M, Poliwczak AR, Duchnowicz P, Koter-Michalak M, Sikora J, Broncel M. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J Pineal Res 2011;50:261-6.

24. Cipolla-Neto J, Amaral FG, Afche SC, Tan DX, Reiter RJ. Melatonin, energy metabolism, and obesity: A review. J Pineal Res 2014;56:371-81.

25. Pakravan H, Ahmadian M, Fani A, Aghaei A, Brumanad S, Pakzad B. The effects of melatonin in patients with nonalcoholic fatty liver disease: A randomized controlled trial. Adv Biomed Res 2017;6:40.

26. Simko F, Pechanova O, Repova K, Azrirova S, Krajirovicova K, Celec P, et al. Lactacystin-induced model of hypertension in rats: Effects of melatonin and captoril. Int J Mol Sci 2017;18:E1612.

27. Simko F, Reiter RJ, Pechanova O, Paulis L. Experimental models of melatonin-deficient hypertension. Front Biosci (Landmark Ed) 2013;18:616-25.

28. Annamalai S, Mohanam L, Alwin D, Prabhuv. Effect of combination therapy of melatonin and orlistat on high fat diet induced changes in lipid profiles and liver function parameters in serum of rats. Obes Med 2016;2:41-5.

29. She M, Deng X, Guo Z, Laudon M, Hu Z, Liao D, et al. NEU-P11, a novel melatonin agonist, inhibits weight gain and improves insulin sensitivity in high-fat/high-sucrose-fed rats. Pharmacol Res 2009;59:248-53.

30. Kedziora-Kornatowska K, Szewczyk-Golec K, Kozakiewicz M, Pawluk H, Czuczejko J, Kornatowski T, et al. Melatonin improves oxidative stress parameters measured in the blood of elderly type 2 diabetic patients. J Pineal Res 2009;46:333-7.

31. Mohammadi S, Shakerhosseini R, Rastmanesh R, Jafarian K, Amiri Z, Jahangir F. Effects of melatonin supplementation on weight and body fat mass percentage in overweight or obese people. J Qazvin Univ Med Sci 2015;19:24-31.

32. de Luis DA, Izaola O, Aller R, de la Fuente B, Bachiller R, Romero E. Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipokine levels and insulin resistance in obese patients along 9 months. J Diabetes Complications 2015;29:950-4.

33. de Luis DA, Izaola O, Aller R, de la Fuente B, Bachiller R, Romero E. Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipokine levels and insulin resistance in obese patients along 9 months. J Diabetes Complications 2015;29:950-4.

34. de Luis DA, Izaola O, Aller R, de la Fuente B, Bachiller R, Romero E. Effects of a high-protein/low carbohydrate versus a standard hypocaloric diet on adipokine levels and insulin resistance in obese patients along 9 months. J Diabetes Complications 2015;29:950-4.