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# Reduction of Melatonin Level in Patients with Type 2 Diabetes and Periodontal Diseases

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## ABSTRACT

Melatonin mainly released from the pineal gland acts as an antioxidant and free-radical scavenger, also enhance the immunity of the body. A growing number of studies reveal a complex role for melatonin in various diseases, including diabetes and periodontal disease. The aim of this study was to determine salivary melatonin levels in patients with type 2 diabetes and periodontal diseases. A total of 30 type 2 diabetic patients, 30 patients with periodontal disease, 30 type 2 diabetic patients with periodontal disease and 30 age- and BMI-matched controls were studied. The periodontal status was evaluated by the Community Periodontal Index (CPI). Salivary melatonin levels were determined by a commercial enzyme-linked immunosorbent assay (ELISA) kit. Salivary melatonin level in patients was significantly lower ($P<0.05$) than controls. Salivary melatonin concentration decreased in type 2 diabetic patients and periodontitis patients, and the lowest levels were found in type 2 diabetic patients with periodontal disease. Based on the results of this study, it can probably be concluded that salivary level of melatonin has an important role in pathogenesis of diabetes and periodontal diseases. It is also worth noting that this factor could probably be used as a pivotal biological marker in diagnosis and possible treatment of these diseases; however further research is required to validate this hypothesis.
**KEYWORDS**: melatonin, type 2 diabetes, periodontal disease, saliva, Iran.

## INTRODUCTION

Melatonin (N-acetyl-5-methoxy-tryptamine) is the main pineal hormone synthesized from tryptophan in a circadian manner. Melatonin has been recently recognized as a potent free radical scavenger and an immunomodulatory molecule. Besides scavenging of free radicals directly, melatonin decrease oxidative stress status indirectly by stabilizing the inner mitochondrial membrane which contain electron transport chain. Melatonin also stimulates antioxidative enzymes including super oxide dismutase, glutathione peroxidase, glutathione reductase, and catalase. On the other hand, melatonin increases the syntheses of nitric oxide which is a pro-oxidative enzyme.[1,2] Furthermore, it's shown that melatonin stimulates the proliferation and synthesis of type I collagen and promotes bone formation. [3]

Oxidative stress is involved in the pathogenesis of some disorders such as periodontal disease and diabetes.[4,5] Periodontal disease is an oral inflammatory process affecting the alveolar bone, gingiva, and periodontal ligament. An important aspect of periodontal disease is free radicals production and imbalance between the oxidant and antioxidant systems. This status may lead to substantial deterioration of the periodontal tissues. [4]

The relationship between periodontal diseases and melatonin level remains unknown. However, melatonin may have implications in periodontal diseases by diminishing oxidative stress, limiting tissue damage, stimulating the immune response and reduction of alveolar bone loss. [6]

Not only the pathogenesis of periodontal disease is contributed with free radicals over-production but also free radicals are involved in pathogenesis of other disorders such as diabetes. Free radicals and oxidative stress are

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notorious for contributing to cell and tissue damage in diabetes. The hyperglycemia which is the backbone of the pathophysiology of diabetes leading to the development of complications through many intertwined cellular pathways like oxidative stress. [5,7] On the other hand, melatonin is contributed to glucose metabolism in addition to having functions as an antioxidant and as an anti-inflammatory agent. [2,8] Evidence exists that processes leading to and regulating the synthesis of melatonin in the pineal hormon and insulin are dependent on the each other in a largely unknown fashion. Most studies conclude that an increased insulin level in type 2 diabetic patients has an inhibitory affects on the pineal gland and melatonin. In another word an antagonist function has to be assumed between insulin and melatonin. Such data suggest that the pineal gland and its melatonin-synthesizing machinery are sensitive to changes in insulin levels. Some results showed that higher glucose and insulin levels are associated with lower melatonin levels in type 2 diabetic patients. According to the above-mentioned principal components may constitute a hypothetical feedback-connection, which links the insulin- and melatonin-producing organs. [9-11] Despite a large number of studies, the role of melatonin on glucose metabolism is rather controversial. Further investigations should be performed on animals and humans to clarify the role of melatonin on these disorders.

As mentioned there are reports that a lack of melatonin has effects on diabetes and periodontal disease. According to the free radical theory in diabetes and periodontal disease, the present study was conducted to examine the relationship between melatonin levels as an antioxidant and diabetes, as well as the periodontal disease. To best of our knowledge it is the first time to measure melatonin level in diabetic patients who suffer from periodontal disease.

We hope, the measurement of melatonin levels in saliva enhance our understanding of its role in ethiopathogenecity and pathophysiology of the diabetes and periodontal disease. Also, melatonin level probably to be utilized as a potential marker in the diagnosis and treatment of diabetes and periodontal disease; however there is a need to much more studies to assess its efficacy to be a marker.

## MATERIAL AND METHODS

*Subjects:*

This cross-sectional study was carried out at School of Dentistry, Hamadan University of Medical Sciences (Iran). A total of 120 subjects of both genders (46 men, 74 women), aged between 36 to 56 years (45.7 ± 8.5 yrs) were participated in the study. Participants were fully informed about the study and gave written informed consent. The study protocol was approved by the Ethical Committee of the University and performed in accordance with the Code of Ethics of the World Medical Association according to the Declaration of Helsinki.

Dental and medical history of all participants was in accordance with the criteria of the WHO.[12] Age, gender, weight, height and BMI of each participant were recorded.

The subjects were divided into four groups (age- and BMI-matched), according to the aim of the study. As we wanted to compare salivary melatonin level in patients with diabetes and periodontitis the experimental groups designed as below:

Group 1 (control), composed of 30 healthy subjects (18 women and 12 men, mean age of 45.9±8.29 years); all healthy subjects were in good general health status with no history of systemic disease or clinical signs of type II diabetes and periodontal disease.

Group 2, included 30 patients with type II diabetes (19 women and 11 men, mean age of 45.77±8.02 years),

Group 3, included 30 patients with periodontal disease (18 women and 12 men, 45.07±8.77 years), and

Group 4, composed of 30 patients with type II diabetes and periodontal disease (19 women and 11 men, mean age of 46.33±9.25 years).

The inclusion criteria for patients with type II diabetes were: (a) age between 35 and 65 yr old, and FBS more than 126 mg/dl (b) glycosylated hemoglobin (HbA1c) between 7.6 and 8.0% during the last 6 months, values compatible with a tolerable control of diabetes.

The inclusion criteria for patients with periodontal disease were: 35– 65 years old; and evidence of periodontal disease (e.g. bone loss, pocket depth).

Periodontal status was evaluated using the Community Periodontal Index. [12] Community Periodontal Index, currently recommended by the World Health Organization, consists of dividing the oral cavity into six sextants, with tooth indexing in each. Teeth index are 17/16 for the first sextant, 11 for the second, 26/27 for the third, 36/37 for the fourth, 31 for the fifth and 47/46 for the sixth. Teeth were examined using a probe with two marks located at 8.5 and 11.5 mm. The Community Periodontal Index codes used for recording periodontal status were as follows: code 0, healthy periodontium; code 1, moderate bleeding; code 2, presence of supra- or sub-gingival dental calculus; code 3, periodontal pocket of 4-5 mm; and code 4, periodontal pocket of 6 mm or higher. The same dentist performed all examinations. A concordant diagnostic analysis was performed on 12 randomly selected patients by a second examiner, yielding an interobserver concordance coefficient of 81% for CPI assessments.

Exclusion criteria included the presence of other concomitant systemic disorders (such as epilepsy and schizophrenia) and diseases which may affect the immune system, such as chronic infectious and neoplastic processes. Patients under pharmacologic treatment that could alter melatonin levels were also excluded from the study.

Data were assessed by a single-masked examiner. The intra-examiner reliability was calculated to be 84%.

*Saliva collection*

Patients and controls came to the School of Dentistry of the Medical University of Hamadan at 09:00 AM after 12-h overnight fast. After 20 min of rest, a sample of saliva was obtained from each individual. In order to stimulate salivary secretion, the participants chewed a piece of paraffin wax for 7 min. Saliva produced during the first 2 min was discarded and then during the following 5 minutes saliva was collected to avoid any possible contamination. The patients chewed the paraffin during the time of saliva collection. Samples of collected saliva were centrifuged at 3000 g, 4ºC for 15 min, and then the clear supernatant was frozen at -80ºC until assays were performed.

Salivary melatonin assay

The melatonin levels were analyzed in duplicate using commercially available ELISA kits (Direct Saliva Melatonin ELISA; EK-DSM, Switzerland), and the mean values of the duplicates were used for analyzing the results. The kit sensitivity was 0.5 pg/mL. The intra- and inter-assay coefficients of variation were 12.6% and 22.9%, respectively.

Determination of FBS and HbA1c:

All participants reoffered to the laboratory at 09:30 AM and were seated for 30 min before sampling. Blood samples (5-7 mL) were collected from the antecubital vein and centrifuged at 3000 g for 10 min, followed by separation of the plasma fraction, which was then frozen (-20 C) until assay. The levels of glucose in plasma and HbA1c in whole blood were measured in all study groups by BT-3000 autoanalyzer.

*Statistical analysis*

Means and standard deviations were calculated for the following study variables: patient age, CPI, salivary melatonin, FBS and HbA1c. For multiple comparisons analysis of variance was used. If the ANOVA test showed significant difference further post hoc Tukey or Dunnet test was applied. The statistical significance of associations among variables was determined by using the Spearman correlation coefficient. Statistical significance was set at p value of less than 0.05. The Statistical Package for the Social Sciences (SPSS) (version 16.0) was used for the analysis of data.

## RESULTS

Table 1 shows the comparison among patients and healthy individuals. All groups of participants (46 males and 74 females) were matched for age and body mass index (BMI) (table 1). The BMI was calculated according to the standard formula.

In all subjects' glucose, HbA1c and melatonin levels and also CPI index were assayed.

The comparison of serum levels of glucose and HbA1c among patients and healthy controls is illustrated in Table 1. Patients with diabetes (group 2,4) had significantly higher mean levels of glucose (160.87±31and 165.30±34.2 mg/dl respectively) ($P < 0.05$), and HbA1c (7.74±1.4 and 7.92±1.2 % respectively) ($P < 0.05$) than periodontitis patients and healthy subjects.

The CPI for group 3 and 4 who had periodontal disease was 2.68 and 2.63, respectively. As expected, the CPI were significantly higher in patients with periodontitis (group3,4), than other groups (group 1,2).

The saliva melatonin concentration were markedly lower in patients groups than in controls ($P<0.05$). In the current study, we observed that the mean saliva levels of melatonin were 9.8±1.9 pg/mL, 5.5±1.7 pg/mL, 5.1± 2.1 pg/mL and 4.9±2.2 pg/mL in controls, type 2 diabetic patients, Periodontitis patients and type 2 diabetic patients with periodontitis , respectively (Figure 1). Although the lowest level of salivary melatonin was observed in type 2 diabetic patients with periodontitis (group 4) there was no significant difference between groups 2 to 4 ($p>0.05$).

Table 1. Comparison of the study variables among the controls and patients.

| Variable | Group1 (mean±SD) | Group2 (mean±SD) | Group3 (mean±SD) | Group4 (mean±SD) |
|---|---|---|---|---|
| **Age (years)** | 45.9±8.29 | 45.77±8.02 | 45.07±8.77 | 46.33±9.25 |
| **BMI (kg/m2)** | 25.96±2.12 | 26.23±2.05 | 26.65±3.01 | 26.98±2.67 |
| **FBS (mg/dl)** | 110±8.00 | 160.87±31 * | 115±9 | 165.30±34.2 * |
| **Glycated Hemoglobin (%) HbA1c** | 6.1±1.00 | 7.74±1.4 * | 6.3±1 | 7.92±1.2 * |
| **Plaque Index** | 25.43±4.09 | 42.53±9.20 * | 51.77±10.42 * | 46.33±10.95 * |

* Significant difference with Group1 ($p < 0.05$).

Group 1 (control); 30 healthy subjects (18 women and 12 men, 45.9±8.29 years), Group 2; 30 type II diabetic patients (19 women and 11 men, 45.77±8.02 years), Group 3; 30 patients with periodontal disease (18 women and 12 men, 45.07±8.77 years), and Group 4; 30 type II diabetic patients with periodontal disease (19 women and 11 men, 46.33±9.25 years).

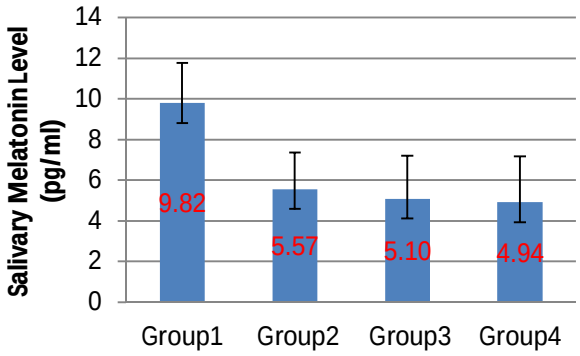


Figure 1. Salivary concentrations of Melatonin (pg/ml) in patients and controls.

*significant differences with group1 ($P<0.05$)

Group 1 (control); 30 healthy subjects (18 women and 12 men, 45.9±8.29 years), Group 2; 30 type II diabetic patients (19 women and 11 men, 45.77±8.02 years), Group 3; 30 patients with periodontal disease (18 women and 12 men, 45.07±8.77 years), and Group 4; 30 type II diabetic patients with periodontal disease (19 women and 11 men, 46.33±9.25 years).

## DISCUSSION

As subjects' ages and BMI were matched, their possible effects are excluded.[15] In the present study we measured melatonin in saliva; assessing salivary melatonin has recently been used as an alternative method for blood analysis since about 24–33% of the plasma melatonin appears in the saliva. Hence, the measurement of salivary melatonin levels represents an indirect, non-invasive procedure for the assessment of plasma melatonin levels which is very useful for the odontologist. [16]

Melatonin selected as an assayed antioxidant in current study, since it's shown that melatonin turned out to be more effective than classical antioxidants to reduce the oxidative stress.[17]

The objective of this study was to evaluate the salivary levels of melatonin as a possible marker in diabetes and periodontal disease. The study population included a group of healthy subjects, a group of patients with type 2 diabetes, a group of patients with periodontal disease and a group of type 2 diabetic patients with periodontal disease. To best of our knowledge it is the first time to examine melatonin level in type 2 diabetic patients with periodontitis. The association between diabetes and periodontal diseases is well-established. Diabetes is a risk factor for periodontal disease, with diabetic patients exhibiting an increased prevalence, extent and severity of gingivitis and periodontitis compared to healthy adults. [18]

As expected, serum concentrations of glucose and HbA1c value were significantly greater ($P<0.05$), in the type 2 diabetic patients (groups 2 and 4) than in the controls and Periodontitis patients (Table-1).

Data from this study indicated that the amount of serum melatonin secreted by salivary glands decreased in patients with diabetes and peridontitis. This finding is in accordance with the results of earlier studies. This result suggests that the melatonin may possess the ability to fight against infection and inflammation, probably due to its antioxidant and immunoenhancing action. Periodontal disease is well known to be associated with an inflammation of the periodontium that destroys periodontal ligament and alveolar bone by resorptive processes. Increase of the oxidative stress in the inflamed area usually triggers the activity of the osteoclast and the bone resorption. Also, free radicals burst coming from the phagocytic cells, migrating to the inflammation place, damage significantly the gingival tissue. [6,19,20]

Previous data have shown the existence of an inverse relationship between per-oxidation products and the quantity of antioxidants in periodontal pathology. A key finding in periodontitis is polymorphonuclear neutrophils

infiltration; these cells produce high amounts of free radicals. Moreover, a massive neutrophil migration to the gingiva and gingival fluid during periodontitis leads to abnormal spreading of free radicals. [4]

In this disease, an additional cause for the decline of melatonin may contribute or be even decisive. The toxic metabolite, 5-aminolevulinic acid, is a free radical-generating compound which leads to oxidative stress. [21] It has been observed that high levels of oxidants can promote increases in the consumption of melatonin, even in organisms producing melatonin in concentrations by orders of magnitude higher than in vertebrates [22], and thus it may indicate that melatonin can be destroyed by free radicals generated at high rates.

The result of current study showed the reduced melatonin level in diabetic patients. To date very few studies about the influence of diabetic situations on the pineal gland exist and it is largely unclear why the melatonin plasma concentration is reduced under diabetic conditions. Noradrenaline is the main stimulus of pineal melatonin synthesis.[23] Earlier investigations illustrated that the pineal glands of diabetic animal model contain less noradrenaline and produce less melatonin in reaction to noradrenaline. The synthesis of melatonin starts with tryptophan, but the absolute amount of tryptophan is reduced in pineal glands of diabetic animals. Tryptophan deficiency can lead to decreased pineal and plasma melatonin concentrations. Other explanation for reducing melatonin in diabetes is that the expression of the melatonin synthesizing enzymes are altered under diabetic conditions and the concentrations of all precursors are reduced in the pineal gland of diabetic animals.[24]

Similar to our results Cutando etal[25] found that the salivary melatonin level was lower in patients with diabetes and periodontitis. Although these two studies have the same results there some differences between them such as matching the age and BMI of all participants which performed in the present study. In the current study the FBS and HbA1c was measured and matched between two diabetic groups.

We assume that an increased insulin level in type 2 diabetes exerts an inhibitory effect on the pineal gland and melatonin, so a functional antagonism between insulin and melatonin has to be suggested.[26] Complementary observations on the type 2 diabetic patients displayed decreased melatonin plasma levels along with raised plasma insulin levels or increased pancreatic MT1- and MT2-receptor expression. [27] The classic membrane associated melatonin receptors, in mammals MT1and MT2, have been found to be present in the pancreas and the islets of Langerhans. It has been determined that the melatonin negatively affects insulin secretion through MT1- and MT2-receptors on the ß-cell surface.[11,28] Together the above-mentioned principal components may constitute a hypothetical feedback-connection, which links the insulin- and melatonin-producing organs.

## CONCLUSION

Based on the results of this study, it can probably be concluded that saliva level of melatonin has an important role in pathogenesis of diabetes and periodontal diseases. It is also worth noting that this factor could probably be used as pivotal biological markers in diagnosis and possible treatment of these diseases, although further research is required to validate this hypothesis.

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