Review Article

J Babol Univ Med Sci
21; 2019. P:249-258

The Role of Melatonin on Metabolic Factors related to Periodontal Disease in Patients with Type 2 Diabetes Mellitus

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J Babol Univ Med Sci; 21; 2019; PP: 249-58
Received: Sep 14th 2018, Revised: Dec 22th 2018, Accepted: Jan 5th 2019.

ABSTRACT

BACKGROUND AND OBJECTIVE: Regarding to various controlling and therapeutic interventions, the risk of periodontal disease in diabetics is three times that of non-diabetics. Because of the central role of oxidative stress in the pathogenesis of diabetes, interest in the use of antioxidants, including melatonin, as a complete therapeutic approach has increased. Therefore, this review study was performed to investigate the role of melatonin on metabolic factors associated with periodontal disease in patients with type 2 diabetes.

METHODS: This review study was conducted on various databases including Scopus, PubMed, Science Direct, Google Scholar and Persian databases such as Magiran and SID and keywords such as type 2 diabetes, periodontal disease, melatonin, hyperglycemia, lipid profile, hypertension, obesity, and Inflammatory factors were carried out from 2000 to 2018.

FINDINGS: A review of studies indicates that melatonin supplementation can reduce progressive damage of periodontal tissue, blood glucose levels, lipid profiles, hypertension, obesity and inflammatory factors in T2DM patients with periodontal disease, and therefore it has a significant role in improving of these patients. On the other hand, it has been shown that increased blood glucose can reduce the production of melatonin from the pineal gland in diabetic patients. Therefore, the supplementation with melatonin in these patients can play a useful role in increasing the production of melatonin in the body by reducing blood glucose levels.

CONCLUSION: The obtained results showed that melatonin supplementation with its antioxidant role can have a beneficial role in improving the survival of T2DM patients with periodontal disease by balancing inflammatory and anti-inflammatory cytokines.

KEY WORDS: *Type 2 Diabetes Mellitus, Periodontal Disease, Melatonin, Lipid Profile, Inflammatory Factors.*

Please cite this article as follows:

Bazyar H, Alipour M, Mirzaee F, Moradi Poodeh B, Zare Javid A. The Role of Melatonin on Metabolic Factors related to Periodontal Disease in Patients with Type 2 Diabetes Mellitus. J Babol Univ Med Sci. 2019;21: 249-58.

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Introduction

Diabetes mellitus (DM) is one of the most important metabolic diseases that its prevalence is increasing worldwide (1). According to the International Diabetes Federation (IDF) report in 2015, about 415 million adults have diabetes and are projected to rise to 642 million in 2040 (2). Despite extensive research on the treatment of diabetes, there is still no definitive treatment for this disease (4, 3). Chronic hyperglycemia as a major feature of DM can affect all organs and systems of the body, including gingival and periodontal tissues (5).

Evidence suggests that there is a bilateral relationship between diabetes and periodontal disease. In this sense, diabetes mellitus is associated with increased prevalence and progression of periodontitis, while periodontal infection is in turn associated with poorer blood glucose control in diabetics (6). The prevalence of severe periodontitis in diabetic patients has been reported to be approximately 39 to 59.6% higher than in non-diabetic patients (7). In general, the risk of periodontal disease in diabetics is three times more than non-diabetics (8).

Periodontal disease is a chronic inflammatory infection that can destroy the supporting tissues by destroying the connectivity of the connective tissue and bone. The pathogenesis of periodontal disease is characterized by the complex relationship between microorganisms in the dental biofilm (plaque) and the host inflammatory immune response that may be influenced by genetic factors, environmental conditions such as smoking and systemic diseases (9). Gingivitis and periodontitis are two common forms of the disease. Gingivitis is characterized as inflammation of the gums without any signs of bone destruction. Periodontitis is defined as clinical and radiographic signs of destruction of tooth support structures.

The main cause of periodontal diseases is microbial dental plaque (10). Gram-negative and anaerobic bacteria actinomycetemcomitans (Aa) A. and P. gingivalis (Pg) are key components in the etiology of periodontal disease (11, 12). Although the bacteria are the initial cause of the disease, most of the gum tissue damage is due to the abnormal response to these microorganisms and their produced materials (12). Severe periodontitis in patients with or without diabetes is associated with increased levels of proinflammatory cytokines and proinflammatory mediators (13). These inflammatory factors may also cause harmful changes in lipid metabolism (14). In general, periodontal disease may decrease serum antioxidant levels and increase the production of free radicals (15). It has therefore been suggested that periodontal diseases may be involved in general inflammation and the development of systemic inflammatory diseases (16).

Therefore, it is important to identify risk factors associated with periodontal disease. Among the various risk factors for periodontal disease, diabetes mellitus is considered to be the most important risk factor (17). Oxidative stress has been found to play a key role in the pathogenesis of both periodontal disease and diabetes (18). Type 2 diabetic patients with periodontal disease have elevated levels of inflammatory factors that can affect blood glucose and lipid metabolism (19). Therefore, due to the central role of oxidative stress in the pathogenesis of diabetes, interest in the use of antioxidants as a complete therapeutic approach has increased (20). Melatonin is one of these antioxidants and eliminates physicochemical properties of free radicals (21). Melatonin (methoxytryptamine -N-acetyl-5) is a lipophilic hormone secreted from the pineal gland. After being released into the bloodstream, it reaches the body's cells and passively spreads through the saliva to reach the oral cavity (22).

The melatonin-regulating effect is almost started in patients with or without periodontitis. Studies have shown that melatonin may neutralize inflammation in the periodontal gum and tissue (23). Melatonin performs a variety of functions, including its possible positive effect on bone, energy metabolism and body weight. Animal studies have shown that daily treatment with melatonin reduces body weight, plasma leptin, adiponectin, triglycerides, cholesterol, insulin, and glucose (24). Thus, melatonin, in addition to acting as an antioxidant and anti-inflammatory agent, is also functionally linked to glucose metabolism (25). Melatonin has been shown to improve insulin resistance and glycemic control in diabetic mice (26). A study by Liu and colleagues showed that melatonin reduced levels of TNF-α, iNOS, IL-1β, and Cox2 in hypoxic mice (27). Melatonin levels in the saliva and plasma of chronic periodontitis patients were significantly lower than in healthy subjects (28).

Various studies have shown that oxidative stress plays a key role in the pathogenesis of both diabetes and periodontal disease. On the other hand, production of lipopolysaccharides by oral bacteria can worsen periodontal disease and impair blood glucose control, which may lead to increased gingival tissue bleeding and delayed wound healing in periodontal disease. It has therefore been suggested that melatonin supplementation could play a bilateral role in controlling both diseases

by targeting oral bacteria and inflammatory parameters. This review study was performed to evaluate the role of melatonin on metabolic factors associated with periodontal disease in patients with type 2 diabetes.

Methods

In this narrative review study, we first identify risk factors associated with periodontal disease and then discuss the effects that melatonin in improvement of periodontal tissue status, blood glucose and lipid profile, blood pressure, obesity and inflammatory factors in patients with type 2 diabetes. Interventional studies examined the effect of melatonin supplementation on periodontal tissue healing were analyzed. Articles were reviewed and extracted by searching reputable English scientific databases such as Scopus and Science Direct, Pubmed and Persian scientific databases such as Magiran and SID between 2000-2018 using keywords: "Periodontal" AND "Diabetes", "Periodontal" AND " Obesity "," Periodontal "and" Blood Pressure "," Periodontal "AND" Lipid profile "," Diabetes "AND" Obesity "," Diabetes "and" Blood Pressure "," Diabetes "and" Lipid profile "," Melatonin " AND "Periodontal", "Melatonin" AND "Diabetes", "Melatonin" AND "Obesity", "Melatonin" and "Blood Pressure", "Melatonin" and "Lipid profile". Related articles investigating the association between periodontal disease with various metabolic factors, studies investigating the role of melatonin supplementation on various factors associated with diabetes and periodontal disease were reviewed, and studies with poor design and poor quality, studies investigating the effect of melatonin supplementation on unrelated factors were excluded. In addition, studies investigating other nutritional supplements in periodontal diabetic patients, and studies that examined the effect of melatonin supplementation on type 1 diabetes were excluded.

Results

Bilateral relationship between periodontal disease and hyperglycemia: Periodontal disease has been found to be associated with increased glycation hemoglobin levels, impaired fasting glucose, and insulin resistance, which could be a bilateral relationship. In fact, there is an increased risk of periodontal tissue destruction that may be related to various factors including increased production and accumulation of advanced glycation end products (Advanced glycation end products = AGEs) in periodontal tissues, increased cellular oxidative stress and production of anti-inflammatory cytokines in serum, saliva and intestinal fluid in patients with chronic hyperglycemia and it may also leads to deleterious effects on secretion and function of Insulin and the development of insulin resistance, especially in response to microbial infections.

In addition, if periodontal disease is left unmanageable and severe, it can lead to longer periods of high blood sugar levels and increase the risk of diabetes complications in the individual (31,32). Rezvanfar et al (26) showed that 6 mg melatonin (2 tablets 3 mg) for 12 weeks in diabetic patients significantly decreased fasting blood glucose and glycated hemoglobin levels (33). In another study, Raygan et al. indicated that taking 10 mg of melatonin for 12 weeks significantly reduced plasma glucose, serum insulin concentration, insulin resistance, and increased insulin sensitivity (34). Balci Yuce et al. revealed that 4 weeks use of melatonin (10 mg/kg/day) decreased blood glucose levels in diabetic rats with periodontitis, but this decrease was not significant (35). Molecular studies have revealed the presence of MT1 and MT2 melatonin receptors in the islets of Langerhans as well as in human pancreatic tissue (36).

Studies show that melatonin may inhibit cyclic AMP (cAMP) and stimulate insulin secretion, which is mediated by the Gi protein that binds to MT1 receptors. Melatonin is an MT2 receptor activator that blocks the second GMP (cGMP) secondary messenger and inhibits insulin secretion by pancreatic beta cells. According to numerous studies, increased insulin levels in T2DM patients may lead to inhibitory effects on the pineal gland and melatonin, so there is a disagreement between insulin and melatonin. These studies show that the pineal glands and their melatonin synthesizers are sensitive to any change in insulin levels. Some studies have shown that high levels of glucose and insulin correlate with low melatonin levels in T2DM. On the other hand, melatonin increases insulin sensitivity, glucose tolerance, and GLUT4 gene expression in insulin-sensitive tissues (such as skeletal tissue and white and brown adipose tissue and heart muscle) (37).

Relationship between periodontal disease and dyslipidemia: In recent years, studies have shown a bilateral relationship between periodontal disease and dyslipidemia. Increased lipid levels have been found to increase the risk of periodontal disease and, in turn,

nflammation caused by periodontal disease has a negative effect on the control of serum lipids (38). Acute systemic or chronic infections are associated with changes in the concentration of cytokines and hormones that alter the metabolism of fats. Also periodontal and accumulation of pathogenic bacteria and endotoxins at the gingival site cause inflammatory reactions in the body and release of inflammatory cytokines such as TNF-α, IL-6 and IL-1b, which can itself promote fat metabolism and lead to chronic hypertriglyceridemia (39). Numerous studies have shown the antioxidant effect of melatonin on LDL oxidation. Due to its lipophilic nature, melatonin can easily enter the lipid core of LDL particles and prevent lipid peroxidation (40). Melatonin can also have a protective effect by increasing endogenous cholesterol secretion (41). Numerous studies support the positive effect of melatonin on lipid profile in diabetic patients. Rezvanfar et al. found that after 3 months of melatonin consumption, HDL cholesterol levels increased significantly, but no significant changes were observed in TG, CHOL, and LDL (33).

The study of Raygan et al. showed that supplementation with 10 mg melatonin daily for 12 weeks significantly increased HDL levels and significantly reduced the ratio of total cholesterol to HDL. But changes in other lipid profile indices were not significant (34). Similarly, Amin et al. showed that treatment with oral melatonin for 21 days in diabetic rats not only significantly increased HDL levels but also decreased levels of CHOL, TG, LDL-C and VLDL (42).

Role of Inflammation in the pathogenesis of diabetes and periodontal disease: Inflammation is known to be a link between insulin resistance, obesity and diabetes. Numerous studies have pointed to the potential role of IL-6, IL-1β and TNF-α in tissue destruction in periodontal disease (43). In fact, microbial plaque produced in periodontal disease plays a prominent role in enhancing the production of pro-inflammatory cytokines and systemic inflammation (44). Patients with periodontitis have high levels of pro-inflammatory cytokines such as IL-1β, TNF-α and an arachidonic acid metabolite such as prostaglandin E2 (PGE2) in the posterior gingival fluid (GCF). PGE2 is a cyclooxygenase pathway metabolite that is the strongest mediator of alveolar bone loss in periodontitis (45). These pro-inflammatory cytokines play a key role in the control of periodontal inflammation. These cytokines are key drivers of the inflammatory and immune response to pathogens. Therefore, the production of proteolytic enzymes and the activity of osteoclastic enzymes as a result of these cytokines are periodontal generating factors (46). It has been suggested that the effects of melatonin on diabetic patients with periodontal disease may be of two types: First, the anti-inflammatory and antioxidant properties of melatonin reduce inflammation in periodontal tissues and, second, melatonin destroys the ROS produced in DM and can therefore reduce the inflammatory effects of diabetes on periodontitis. (48, 47). Thus melatonin could decrease the production of inflammatory factors such as hsCRP, TNF-α and IL-1β through inhibition of NF-κB-dependent cellular pathway phosphorylation that produces inflammatory mediators as well as inhibition of NLRP3 as an important inflammatory compound. (49). Pakravan et al found that taking one tablet of melatonin 2 times daily for 6 weeks significantly reduced serum hsCRP levels in patients with nonalcoholic fatty liver disease (50). Similarly, Cutando et al showed that topical melatonin administration in patients with diabetes and periodontal disease caused a significant decrease in hsCRP and IL-6 serum levels (51). However, Koziróg and colleagues showed that daily 5 mg melatonin administration for 2 months did not significantly decrease hsCRP levels (52). Differences in the type of disease, research method, number of patients and duration of intervention as possible factors have led to variations in results.

The role of obesity in the pathogenesis of periodontal disease: Obesity is one of the most important threats to human health associated with inflammatory diseases such as diabetes and periodontal disease (53). There is a close relationship between the development of periodontitis and an increase in body mass index in obese individuals and inadequate blood glucose control. Obesity can play an important role in the incidence and development of systemic diseases such as periodontal disease with increasing levels of inflammatory factors (54). Obesity (especially visceral obesity) is one of the most important risk factors in T2DM (33). Studies have shown that nutritional factors that control dietary intake can improve metabolic factors associated with type 2 diabetes by controlling obesity (55,56).

It has been suggested that melatonin can inhibit obesity and control weight by regulating energy intake and body fat mass regulation (32). The anti-obesity effects of melatonin are due to its role in regulating energy expenditure through activation of brown adipose tissue and effect on energy balance based on regulation of energy flow from the reserves (57). In obesity, the production of inflammatory factors is increased by adipose tissue, and melatonin, as an antioxidant, blocks

the NF-κB-dependent cellular pathway that produces inflammatory mediators and thereby reduces inflammation (58). Pakravan et al. showed that weight and waist circumference were significantly decreased in the melatonin receiving group during the study period (50). A study by She et al. showed that treatment with melatonin (4 mg/kg) for 8 weeks in obese mice (induced by high-fat diet) significantly reduced weight and other metabolic factors (33).

Relationship between periodontal disease and blood pressure: Hypertension is one of the most important risk factors for the pathogenesis of atherosclerotic cardiovascular disease and has raised concerns about the health of individuals. Recently, "low-grade chronic inflammation" has been identified as a potential cause of hypertension, including pre-hypertension. It is generally accepted that periodontitis is one of the diseases of chronic low grade inflammation. Epidemiologic studies indicate that chronic periodontitis is associated with a high incidence of arterial hypertension. Treatment of periodontal disease along with other blood pressure control treatments can further reduce blood pressure. It has also been shown that vascular endothelial dysfunction, in addition to its important role in the onset and progression of blood pressure, can also promote periodontal disease, so treatment of periodontal disease can also improve vascular endothelial function (59). Some studies have suggested the sympatholytic effect of melatonin and its involvement in the renin-angiotensin system decreases angiotensin II production and treatment with melatonin reduces inflammation in the renal interstitial tissue as measured by lymphocyte and macrophage infiltration. melatonin also increases vasodilatation, decreases sympathetic system activity and reduces levels of catecholamines (epinephrine and norepinephrine) in the blood, increases nitric oxide (NO) production, and also improves baroreceptor reflexes responsible for maintaining blood pressure (60). Możdżan and colleagues found that 5 mg melatonin for 8 weeks significantly reduced SBP and DBP both day and night in type 2 diabetic patients with hypertension (61). Koziróg and colleagues also showed that 5 mg melatonin daily for 2 months significantly reduced SBP and DBP (52).

Decreased melatonin levels in diabetic patients with periodontal disease: Serum and salivary levels of melatonin are reduced in patients with DM and periodontal disease. One possible mechanism for reducing melatonin in periodontal disease is the toxic metabolism of 5-aminololinic acid. This toxic metabolite is a free radical that results in oxidative stress (62). High levels of oxidants may increase melatonin consumption even at high concentrations of melatonin-producing organs (63). On the other hand, in diabetic patients, noradrenaline is the main driver of melatonin synthesis in pineal gland (64). Pineal glands in the diabetic animal model have less noradrenaline and produce less melatonin in response to noradrenaline. In fact, melatonin synthesis begins with tryptophan, however, the net concentration of tryptophan in the pineal glands of diabetic animals is reduced. Consequently, tryptophan deficiency may decrease pineal and plasma melatonin concentrations (65). In general, it has been suggested that the combination of diabetes and periodontal disease may lead to a further decrease in melatonin levels. Rybka and colleagues showed that daily 5 mg melatonin administration for 1 month significantly increased serum melatonin (66).

The effect of melatonin supplementation on periodontal disease: Limited interventional studies have been performed on the role of nutrients and oral health. In a study by Cutando et al., after topical application of melatonin, a significant decrease in gingival index and pocket depth was noted (51). Numerous studies have shown the beneficial effects of melatonin and its physiological and pathological consequences in the oral cavity (22). Gülle and colleagues reported that melatonin can improve the pathogenicity of periodontal inflammation in the rat (67). Similarly, topical use of melatonin in diabetic patients reduced the progression of periodontal caries due to a decrease in the regulation of pro-inflammatory factors (68). Balci Yuce et al. showed that melatonin reduces osteoclast cells, thereby reducing alveolar bone loss and periodontal destruction in rats with periodontitis. But it does not affect periodontitis without DM in rats (35).

In addition, studies have suggested that melatonin has antimicrobial effects against p. gingivalis streptococcus mutans and prevotella intermedia, which are considered as two major bacteria in the pathology of periodontal disease (69). Melatonin may also have antioxidant activity and directly affect free radicals or indirectly inhibit ROS production (70). In addition, to prevent osteoclastic activity, melatonin affects osteoblast proliferation and alkaline phosphatase activity. Melatonin also increases gene expression of osteoblastic activity indices of osteocalcin, osteopontin, sialoprotein, and type I collagen, stimulating

mineralized matrix formation and stimulating new bone formation (71). Therefore, it can be said that there is a relationship between periodontal disease and various types of systemic damage such as DM. It is hypothesized that controlling one of these two pathologies may be useful in controlling the other (72).

Side effects of high dose melatonin supplementation: Although melatonin is not toxic, the least effective dose should be used to prevent overuse. The doses used for clinical studies on the effects of melatonin vary from 1 to 10 mg daily (73). However, some adverse effects such as dizziness, headache, nausea, and drowsiness have been reported with high doses of melatonin, which have been used to treat some diseases (74).

Discussion

Diabetes is a chronic disease that can affect patients' quality of life due to damage to various organs such as heart, kidney, eyes, gum tissue and teeth. Therefore, caring behaviors such as diet modification, physical activity, and drug therapy can be effective in controlling the acute and long-term complications of this disease and can improve the quality of life of these patients (75). Periodontal disease is one of the complications of diabetes, and various studies have shown that toxins produced by anaerobic gram-negative bacteria play important roles in the pathogenesis of the disease by producing inflammatory mediators (11). According to the findings of the present study it can be said that since the secretion of these inflammatory cytokines increases the blood glucose levels and consequently decreases the secretion of melatonin and leads to dysfunction of the pineal gland, this increase in blood glucose levels can increase the risk of periodontal disease and increase in bleeding and gum disease. Therefore, given the reciprocal relationship between these two diseases, it can be hypothesized that targeting these cytokines by monoclonal antibodies may restore pineal gland function and increase melatonin levels and result in better control of metabolic factors associated with periodontal disease and therefore result in preventing the progression of diabetes and reduce the risk of periodontal disease, and it may be possible in the future to work on this hypothesis to take an effective step to improve diabetes patients with periodontal disease.

Acknowledgment

Hereby, we would like to thank the Student Research Committee of Ahvaz Jundishapur University of Medical Sciences for supporting this research.

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