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Review

Melatonin and periodontal tissues: Molecular and clinical perspectives

Agata Rita Carpentieri[a,b,*], María Elena Peralta Lopez[a,c], Javier Aguilar[d,e], Verónica Mariana Solá[a]

[a] Cátedra "B" de Química Biológica, Facultad de Odontología, Universidad Nacional de Córdoba, Córdoba, Argentina
[b] INICSA/UNC-CONICET, Enrique Barros esquina Enfermera Gordillo, Ciudad Universitaria, Córdoba, Argentina
[c] Cátedra de Clínica Médica II, Hospital San Roque, Facultad de Ciencias Médicas,UNC, Córdoba, Argentina
[d] Instituto Dr. José M. Vanella, Facultad de Ciencias Médicas, UNC, Córdoba, Argentina
[e] Cátedra "B" de Introducción a la Física y Química Biológica, Facultad de Odontología, UNC, Córdoba, Argentina

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ABSTRACT

Periodontal disease is a frequent chronic inflammatory pathology that implies the destruction of the tissues supporting the teeth, which represents a high sanitary cost. It usually appears associated with other systemic conditions such as diabetes, metabolic syndrome, depression and Alzheimer disease among others. The presence of melatonin and its receptors in the oral cavity supports the hypothesis that this hormone could play a role in homeostasis of periodontal tissues. In the present review we will discuss the potential role of melatonin, a circadian synchronizing hormone, with proved antiinflammatory and antioxidant profile, in the pathogenesis and treatment of periodontitis. Particular emphasis will be placed on the role of the indolamine in the treatment of periodontal disease when this oral condition is comorbid with other pathologies that would also benefit from the therapeutic potential of melatonin and its analogs through diverse mechanisms.

Contents

* Corresponding author.
E-mail address: arcarpentieri@hotmail.com (A.R. Carpentieri).

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1. Introduction

Melatonin (MEL), (N-acetyl-5-methoxytryptamine) is a natural hormone produced in different organs such as retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes and skin but mainly in the pineal gland, where is synthesized in a circadian manner, showing the highest levels of secretion at night, in most species [1]. Pineal production of MEL is the result of a series of well-known reactions [2]. Circadian information related to light/dark environment is transmitted through retino-hypothalamic tract to suprachiasmatic nucleus. This central rhythm generator, in turn, sends a stimulus to the upper thoracic cord and superior cervical ganglia, and through postganglionic sympathetic fibres to the pineal gland, thus determining the polysynaptic activation of beta-adrenergic receptors [3]. Finally, this neural signal is translated into activating the endocrine MEL synthesis pathway, in which the activity of the enzyme arylalkylamine *N*-acetyltransferase (AA-NAT), a key enzyme in MEL biosynthesis, is increased from 30 to 70 times at night and it constitutes a rate-limiting step [4].

Most of MEL actions are mediated by its G protein-coupled membrane (MT1 and MT2) as well as its nuclear (RZR/ROR) receptors [5]. MT1 receptor is present in the brain, cardiovascular system, immune system, testes, ovary, skin, liver, kidney, adrenal cortex, placenta, breast, retina, pancreas and spleen [6]. MT2 receptor, 60% homologous to MT1 receptor, shares the distribution with MT1. There is a MEL-related receptor GPR50, an orphan receptor which Exhibits 45% amino acid homology to MEL receptors. Although MEL does not bind to GPR50, this receptor may heterodimerize with the MT1 receptor, inhibiting its activity [7]. All the commercialized melatoninergic drugs act on both types of receptors without significant selectivity [8]. A third receptor, MT3, with low affinity for MEL and not-coupled to G protein, has initially been found in hamsters and rabbits. It has been reported that this MT3 is analogous to human quinone reductase II and it may contribute to some antioxidant and protective effects of the indolamine [9]. MEL can also bind to nuclear retinoid orphan receptors: ROR and RZR [10]. In addition, several important effects of MEL are displayed without receptor involvement. The pineal hormone passes freely through membranes and reaches all body compartments, whereas MEL synthesized in retina, intestine and other tissue apparently acts locally, in a paracrine way [11].

This hormone regulates important physiological and pathological processes. By binding to its membrane receptors, MEL modulates seasonal and circadian rhythms, acting as an effective synchronizing agent in several situations, such as maternal-fetus entrainment [12], dissociated circadian rhythms induced by a short light–dark cycle [13], insomnia and jetlag [14]. MEL also reduces oxidative stress: directly by scavenging reactive oxygen and nitrogen species and indirectly by stimulating antioxidant enzymes while suppressing pro-oxidant ones. This action diminishes lipid and protein peroxidation [15]. The high levels of MEL in mitochondria could explain its antiapoptotic and antioxidant properties. The indolamine also contributes to protect DNA integrity by activating DNA reparation enzymes [16]. In addition, it modulates immune responses, body weight, reproduction, bone metabolism and tumor growth [17].

MEL synchronizing properties, its anti-inflammatory and antioxidant effects and its immune modulation capacities together with its pharmacokinetic and pharmacodynamic profiles are key characteristics that justify the therapeutic use of this hormone as well as some synthetic analogs for the treatment of various conditions such as diabetes, metabolic and cardiovascular diseases, sleep disorders, Parkinson, affective disorders, chronic inflammatory diseases and cancer among others, be it as monotherapy or as an add-on drug together with other pharmacological agents [18]. In the present article we review the relationship between MEL and different conditions affecting the oral cavity, be it primarily or secondary to other diseases such as diabetes and psychiatric disease among others, discussing the potential benefits of its therapeutic use.

2. Melatonin in the oral cavity and periodontal diseases

Ubiquitious MEL is also present in oral cavity. MEL level in saliva is one-fourth to one-third of the level in blood circulation and ranges from 1 to 5 pg/ml during daytime to 50 pg/ml after midnight peak [19]. Salivary MEL is believed to derive from the unbound melatonin present in systemic circulation which, being a lipophilic molecule, passively enters the cells of the major salivary glands. However, Shimozuma et al. [20] have recently identified the expression of AA-NAT in major salivary rodent and human glands, which suggests that MEL could also be synthesized locally in this tissue. The presence of both MT1 and MT2 receptors in salivary gland ducts and acini, oral epithelium, fibroblasts of the mucosal lamina propria and osteoblasts of maxilar alveolar bone among other oral cells, has been confirmed in different studies [5,21,22]. The importance of MEL in salivary fluid and its precise effects in oral cavity remain to be studied in depth.

Periodontal disease is one of the most common oral infectious conditions among humans, gingivitis and periodontitis being the two major forms of this pathology. It implies the destruction of the tissues supporting the teeth (gingiva, periodontal ligament, radicular cement and alveolar bone) due to the accumulation and maturation of oral bacteria as well as the subsequent immune response displayed by the host [23]. According to Chapple [24], periodontitis is defined as a "complex heterogenic biological phenomenon, derived from the interaction between genetic and epigenetic factors together with environmental determinants that lead to a dysbalance of oral microbiome homeostasis and an inadequate imunitary response". This condition is aggravated by an overproduction of reactive oxygen species (ROS) that leads to peroxidation of membranes, damaging cellular structures [25]. Once established, this condition evolves with reduction of collagen fibres, loss of the attachment to the radicular surface and resorption of alveolar bone [26], eventually causing teeth loss.

There are evidences that MEL could improve periodontal status. Almughrabi et al. [18] examined the association between daytime salivary MEL levels and the severity of the inflammatory status in 70 subjects with periodontal disease. Patients with chronic and aggressive periodontitis had lower levels of MEL both in gingival crevicular fluid and saliva than patients with mild gingivitis and healthy subjects. Similar results were obtained by Bertl et al. [27], who also found that non surgical periodontal therapy resulted in a recovery of the decreased salivary MEL levels in patients with periodontitis. Cutando et al. [28] reported an inverse correlation between plasma and salivary MEL levels and the severity of periodontitis, suggesting that MEL is consumed when scavenging free radicals generated by inflammation. Interestingly, Lodhi et al. [29] found opposite results, being MEL higher in those patients with the most severe inflammatory status. These elevated salivary levels could be the result of compensatory protective mechanism to fight inflammation of the gingiva. More studies including wider populations to assess this variable would be welcome. In any case, salivary MEL could act as a diagnostic biomarker in periodontal disease [30]. Analogous results were reached in animal models. Kara et al. [31] found an improvement of periodontal status with reduced inflammatory cytokines, lower oxidative stress parameters and less periodontal destruction, in rats treated with MEL after periodontitis induction. Similarly, Köse et al. [32] demonstrated a recovery of oxidative stress after inflammation triggered by radiotherapy (Fig. 1).

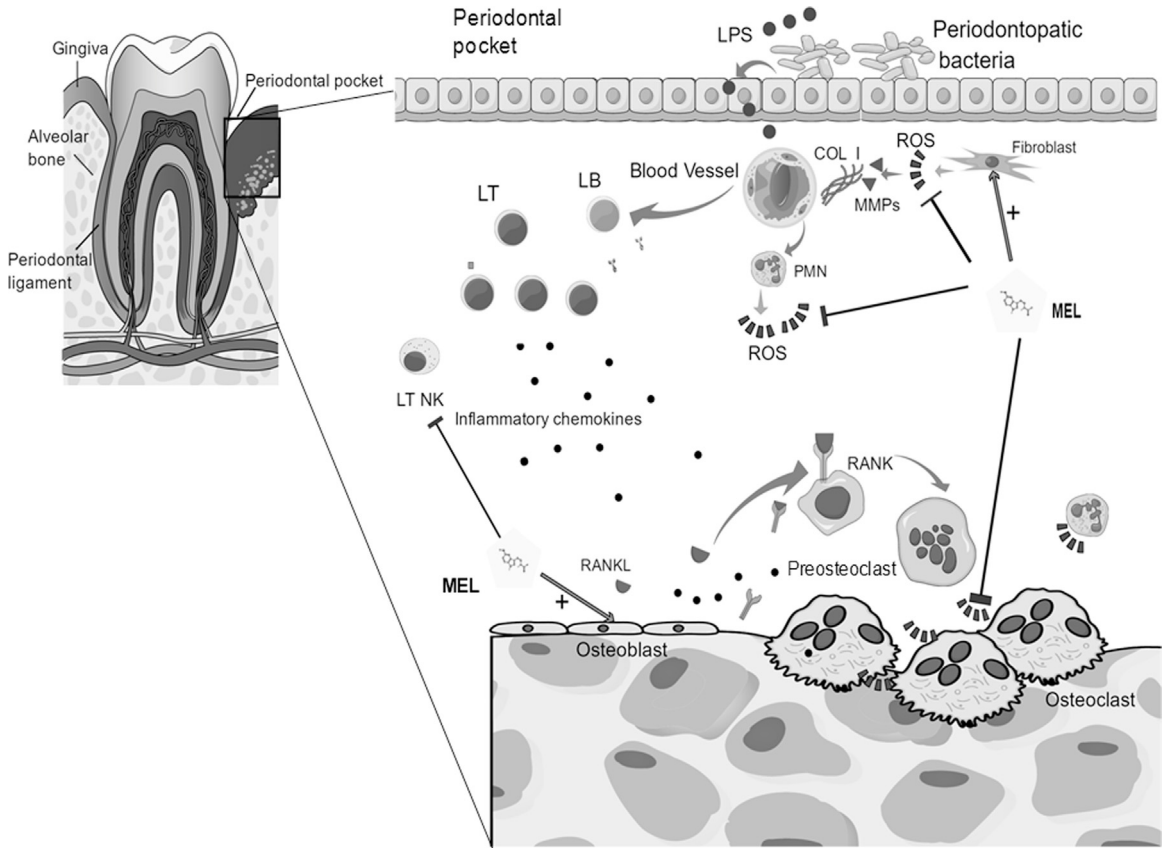

Fig. 1. Melatonin actions on periodontitis pathogenesis. MEL protects periodontal tissues against inflammatory injury by impairing recruitment of PMN, inhibiting MMPs, scavenging ROS and reducing osteoclastic activity while stimulating osteoblasts. PMN: Polymorphonuclear, MMPs: Matrix metalloproteinases; COL I: collagen type I, LB: lymphocyte B; LT: lymphocyte T; NK: natural killer.

3. Melatonin and alveolar bone and dental implants

Bone remodeling is responsible for bone mass maintanance, adjustment of bone strength and/or mineral homeostasis along human lifespan [33]. It is known that MEL affects bone metabolism by a dual effect on osteoblasts (OB) and osteoclasts (OC). In diverse studies, MEL proved to induce human marrow pluripotent stem cells (hMSCs) and preosteoblast into mature osteoblasts. Moreover, MEL reduced hMSCs period of differentiation into osteoblasts from 21 days to 12 days [34–40]. On the other hand, OB has a fluid communication with OC to encourage and maintain bone mass stable [41,42]. This coordination is directed by signals that comprehend bone morfogenetic proteins, transforming growth factor β, insulin-like growth factor 1 and 2, fibroblast growth factor and platelet derived growth factor, between others. These factors are released from the bone matrix through active bone resorption or are fabricated from OB along with macrophage colony-stimulating factor, receptor activator for nuclear factor κ B ligand (RANKL), promoting the fusion of mononuclear cells to form multinucleated OCs [43]. OCs dissolve bone matrix by secreting cathepsin K and tartrate-resistant acid phosphatase [44–46]. These cells also contain superoxide dismutase and produce ROS in the microenvironment of bone which contribute to damage certain components such as collagen or hyaluronic acid. MEL acts in OC lacuna, due to its antioxidant properties [47,48] and its ability to neutralize reactive species, thereby inhibiting bone resorption, protecting structural molecules (Fig. 2).

This protector effect of MEL is particularly relevant in the case of dental implants. This surgical procedure triggers an inflammatory response and bone necrosis around the implant may occur [49,50]. Leukocytes and macrophages increase ROS in peri-implant environment, promoting bone resorption by the OC [37]. MEL antioxidant and anti-inflammatory properties may attenuate this reaction and limit the production of ROS [51–53], and consequently bone resorption, after implant placement. On the other hand, osteointegration is a critical issue after implant placement [54]. Several studies performed by Calvo et al. [55,56] demonstrated that MEL increases osteointegration around implants, especially in the first 2 weeks after surgery. The osteogenic, antioxidant and anti-inflammatory effects of MEL support the potential therapeutic use of the indolamine after implant.

4. Melatonin and periodontal disease in diabetic patients

Salivary level of MEL plays a role in the pathogenesis of diabetes and periodontal diseases. Diabetes mellitus (DM) is a heterogeneous group of disorders, characterized by high blood glucose levels due to a lack of secretion or a defect in the functionality of insulin. These alterations lead to a myriad of complications through diverse cellular and molecular pathways, such as oxidative stress [57,58]. Apart from the well-established functions of MEL as an antioxidant and anti-inflammatory agent, this indolamine exerts an important role in glucose metabolism [59]. It has been described that the synthesis of the pineal MEL and the pancreatic insulin depends on one another in a fashion that remains to be elucidated [60]. It has been confirmed that the treatment with MEL decreases insulin secretion. The synthesis and secretion of both hormones are linked by a circadian manner. In rats, during day phase, high insulin levels are detected when MEL levels are reduced whereas low levels of insulin coupled with high glucose levels are present during the night when MEL levels are increased. In addition, studies in rats

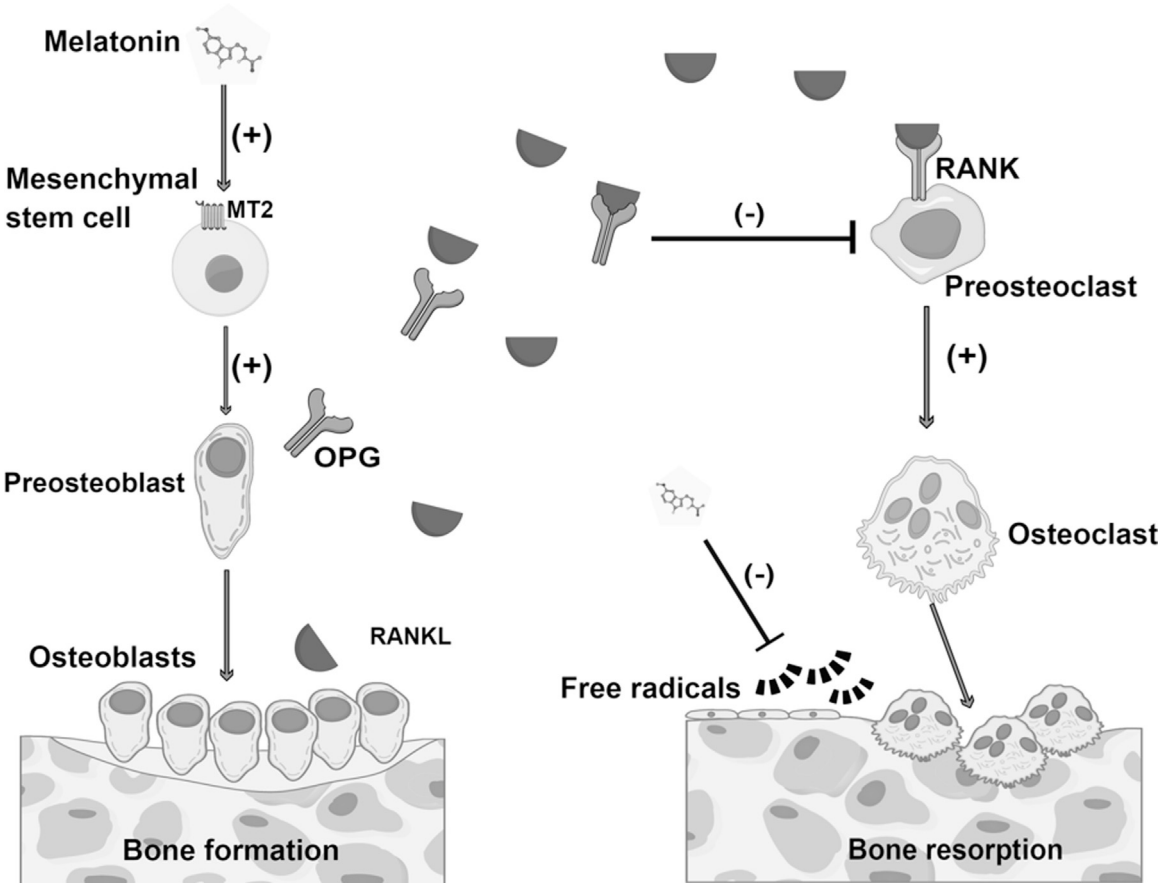

Fig. 2. Effects of Melatonin on bone. MEL induces mesenchymal stem cells differentiation into osteoblasts via MT2 MEL receptors. It also favours osteoprotegerin (OPG) expression in preosteoblasts, which blocks RANKL (receptor activator of NFκB ligand) thus suppressing osteoclastogenesis. MEL prevents radical induced loss of osteoblasts and osteoclasts through its free-radical scavenging and antioxidant properties.

have shown a decline of MEL synthesis with aging, whereas the synthesis of insulin increases. Recent studies show that MEL levels are reduced in diabetic hamsters, and that substitution with MEL would contribute to prevent diabetes. On the other hand, pinealectomy increases the risk to develop diabetes [61].

Several studies suggest that periodontitis impairs an adequate control of glycemia, leading to diabetes descompensation. There is evidence that primary periodontal therapy improves glucose serum levels [58]. Diabetic patients present an imbalance in periodontal tissues, which are characteristically affected. The initial pathogenetic event of diabetes mellitus is the formation of advanced glycation end products by the non-enzymatic reaction of glucose and other glucose-derived compounds with proteins, lipids and DNA. Deterioration in neutrophil activity with a reduced chemotactic response to chemokines and a deficient phagocytic activity together with a hyper-inflammatory response is also observed. [62–64]. Proinflammatory chemokines such as interleukin-1β and tumor necrosis factor-α are augmented in serum of patients with periodontal disease [65]. MEL influences the diurnal rhythms of leukocyte proliferation, cytokine production, and natural killer cell activity [2,66–70], showing antiinflammatory effect in this disease. It is also known that cytokines delivery in inflammated periodontal tissue can stimulate collagenolytic enzyme production and bone resorption [71,72], thus contributing to periodontal tissue destruction. Besides the complications mentioned above, diabetes affects bone metabolism. Type 1 and 2 diabetes are associated with low bone mineral density and a higher risk of low energy fractures [73,74]. This skeletal fragility in diabetic patients could be partially explained by a reduction in bone turnover rate, which determines that older bone is not replaced by new one. This may be related to a decreased osteoblast activity [75] by advanced glycosylation end products induced apoptosis through the MAP kinase pathway [76] MEL has been found to prevent apoptosis inhibiting this pathway [77]. On the other hand, MEL significantly inhibited hyperglycemia-induced oxidative stress and alveolar bone loss through antioxidant effects in OCs of rats with DM and periodontitis [32]. In an investigation performed by Cutando et al. [78], diabetic and no diabetic patients with periodontal disease where treated only with topical application of MEL. This treatment showed an improvement in the gingival index and pocket depth, and a reduction of acid and alkaline phosphatase enzymes, which were elevated in patients with periodontal disease with active bone destruction (Fig. 3).

Both local and systemic treatment with MEL could be useful to improve periodontal status in diabetic patients. This treatment could benefit not only local oral environment but also could contribute to ameliorate glucose levels, helping to prevent chronic diabetes complications.

5. Melatonin and periodontal disease in psychiatric disorders

Melatonin has proved beneficial in the treatment of different psychiatric disorders, particularly those in which the circadian disruption plays a central role, as it is the case of primary or secondary sleep disturbances [79]. This therapeutic use finds its justification in the well-established synchronizing properties of

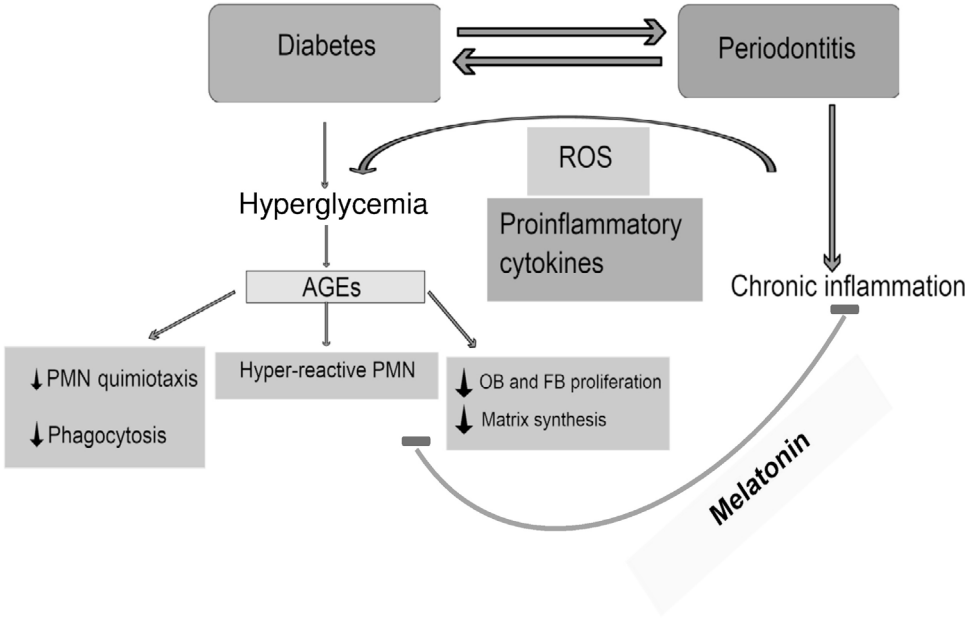

Fig. 3. Melatonin actions in periodontitis associated to diabetes. MEL could improve periodontal status in diabetic patients, due its antiinflammatory properties.

the indolamine. In this same line, some synthetic agonists of MEL receptors, such as agomelatine, ramelteon and tasimelteon, have proved beneficial for the treatment of these various sleep disorders [80]. Besides this circadian property, MEL has managed to lower blood pressure among bipolar disorder patients and to improve lipid profiles and body composition as well as attenuate weight gain among both schizophrenic and bipolar disorder patients. Ramelteon showed a significant efficacy in lowering total cholesterol level. This metabolic effect makes of MEL and its agonists an interesting therapeutic add-on option for the treatment of those patients receiving atypical antipsychotics [81]. Similarly, a myriad of recent studies focusing on the immune-inflammatory component of many psychiatric disorders has emerged. This new interest places melatonin as an important therapeutic strategy given its antiinflammatory and immune-modulatory actions [82].

The association between psychiatric disorders with poor oral health in general and with periodontal disease in particular, has been recurrently described since the fifties. Patients treated for mental illnesses show higher caries index, salivary secretion disorders, gingivitis and periodontitis, compared to the general population. These oral conditions are usually aggravated by frequent comorbidities such as smoking, alcohol and substance abuse, metabolic syndrome, diabetes and nutritional deficiencies among others. Xerostomia is an expected psychotropic side-effect of many antipsychotic drugs, which also contributes to periodontal disbalance [83]. Early studies underlines the social factors implicated in the association of mental and odontological disorders such as difficult financial conditions and inadequate education concerning oral hygiene, together with individual behavioral factors often present in psychiatric patients such as self-care impairment and lack of motivation. More recent studies, however, focus on molecular etiopathological links that could explain this frequent association [84].

In this respect depression is an emblematic example. It is well known that both major depressive disorder and periodontal disease produce an imbalance in proinflammatory cytokine production with increased cytokine levels in the gingival crevicular fluid [85] and reduced circulating cytokines. Depression can also down-regulate the cellular immune response, thus promoting prolonged infection and delayed wound healing that can in turn reinforce the sustained production of cytokines. Interestingly, fluoxetine, antidepressant that selectively inhibits serotonin reuptake, improved periodontitis in a rat model [86]. Similar successful results were obtained in a study including more than 200 patients with chronic periodontitis and clinical depression, in which fluoxetine treatment was associated to lower risk of attachment loss and gum bleeding on probing [87]. Taking into account that melatonin has proved effective as coadyuvant in antidepressive treatment, especially in patients with comorbid sleep disorders such as insomnia [88] or in patients with a strong seasonal component, depressive patients could benefit from the exogenous administration of the hormone which apart from restoring sleep and improving depressive symptoms by a receptor-mediated mechanism it could also have a positive effect on periodontal disease due to its antiinflammatory and immune enhancing effects previously discussed [78]. Its high tolerability allows to co-administer it with other drugs such as fluoxetine, thus potentiating both antidepressant and anti-inflammatory effects. This evidence is of paramount importance since according to epidemiological studies five patients who visits dentist experiences clinically significant symptoms of depression which often remain unsearched by routine dentist anamnesis [89].

Periodontal disease has also been associated with higher brain amyloid load in normal elderly as well as with higher risk of Alzheimer disease (AD) [90]. A positive correlation has been found between serum IgG levels to common periodontal microbiota and risk for developing sporadic AD [91] favouring the possibility of using it as a biochemical predictor of AD. Some groups have suggested that tooth loss could function as a clinical predictor of cognitive impairment [92]. Both Alzheimer disease and periodontitis have chronic systemic inflammation as a common denominator. AD is characterized by local inflammation represented by the formation of extracellular amyloid β-peptide plaques and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein, with consequent microglial activation and increased production of cytokines leading to neurodegeneration while periodontitis, an ubiquituous oral infection associated with gram

negative anaerobic bacteria, can be considered as a "low-grade systemic disease" due to the release of proinflammatory cytokines into circulation and C-reactive protein elevation [93]. It is in this context of chronic local and systemic inflammation that melatonin can prove effective when AD and periodontitis are comorbid. Appart from helping to improve some specific symptoms of AD related to the chronobiological disruption that these patients usually present, mainly in the form of insomnia and related sleep disorders, melatonin can operate as antiinflammatory molecule enhancing the immune response.

6. Conclusions and perspectives

MEL's antioxidant, anti-inflammatory and immune-modulatory properties together with its osteogenic actions on maxillar bone metabolism determine that this indolamine could represent a good therapeutical strategy to treat periodontitis. The potential of this therapeutic use of MEL widens when this oral inflammatory process appears in the context of other systemic conditions that could benefit from one or more of the various effects of this versatile molecule, be it due to its circadian properties or as a result of its citoprotective actions in different tissues other than the oral cavity. Apart from the described versatility of its actions, other advantageous aspect of MEL is that it can be easily combined with other drugs due to its relative safety and low rate of adverse effects. Many aspects of the possible therapeutic contributions of MEL and its agonists remain to be elucidated and both basic studies and clinical trials concerning this issue would be wellcome.

Author contributions

All authors participated in the conception, design, and performance of the study as well as interpretation of data and drafting the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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