MELATONIN AND PERIODONTITIS – A SYSTEMATIC REVIEW AND META ANALYSIS

ABSTRACT

Background: Periodontits is a chronic oral diseases that includes bacterial colonization, inflammation and oxidative stress. Melatonin, a hormone which has antioxidant properties reduces gingival inflammation and oxidative stress.

Aim: The aim of the study is to systematically review the association between melatonin and periodontitis.

Methods: A comprehensive literature search of the following databases were done which included studies of The Cochrane database of systematic reviews, PubMed, pubmed central, Google scholar, research gate , The studies were selected by titles and abstracts based on the search strategy described previously. Then, the full texts of the potentially eligible studies were read and selected based on the inclusion criteria (PICOS criteria).

Results: The meta analysis showed that the mean difference between the salivary melatonin levels in healthy and periodontitis groups was statistically significant with P<.001 Heterogeneity between the studies is 49%.

Conclusion: This systematic review and meta analysis concludes that salivary melatonin level in participants with periodontitis is significantly lesser when compared to the healthy individuals. Supplementation of melatonin improves the periodontal condition.

Keywords: Melatonin, Periodontitis, Oxidative stress, Systematic review.

INTRODUCTION

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.[1] According to Chapple, 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"[2]. Once established, this condition evolves with reduction of collagen fibers, loss of the attachment to the radicular surface and resorption of alveolar bone, eventually

causing teeth loss[3]. This condition could be reversed by a hormone called melatonin. The actions of melatonin as an anti-inflammatory and antioxidative agent could be beneficial, particularly when placed directly in the mouth, to abate the severity of inflammation of the gingiva and periodontium.[4]

Melatonin (MEL), (N-acetyl-5-methoxytryptamine) was discovered in extracts of the bovine pineal gland and synthesis in this organ was determined in 1958[5]. It is a natural hormone though produced in different organs such as retina, gastrointestinal tract, bone marrow, leukocytes, lymphocytes and skin, the main production comes from the pineal gland, where is synthesized in a circadian manner, showing the highest levels of secretion at night, in most species.[6] 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 [7].

Melatonin has multiple, diverse physiological functions. Some of these actions are mediated by specific receptors in the membranes of most, if not all, cells. Melatonin also has receptor-independent free radical scavenging actions. Finally, melatonin has indirect protective functions against reactive oxygen (ROS) and reactive nitrogen species via its ability to stimulate antioxidative enzymes. The combination of the direct and indirect antioxidative actions of melatonin assists this molecule in potently resisting oxidative damage throughout the body, including in the oral cavity.[4] Melatonin, as well as several of its metabolites that are formed when melatonin neutralizes toxic free radicals, are highly effective in reducing oxidative damage to tissues via receptor-independent actions[8]. Because of these combined reactions, which have come to be known as melatonin's antioxidant cascade, melatonin is highly efficient at detoxifying a number of reactive species and thereby reducing the cellular and molecular damage meted out by partially reduced oxygen species [9]. This has many implications for tissues of the oral cavity where oxidative stress is common.

The lamina propria of the gingiva and periodontium often contains numerous immunocompetent cells. Melatonin, a well-known promoter of the immune system, as well as its metabolites N1 -acetyl-N2 -formyl5-methoxykynuramine and N1 -acetyl5-methoxykynuramine, have significant anti-inflammatory actions. Immunocompetent cells also produce their own melatonin. Considering that

inflammation is a major determinant of oral health, orally available melatonin could have a role in reducing gingival inflammation.[4] 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 suggestive of the presence of association between melatonin and periodontal tissues. Numerous studies have been published showing the possible association between the both. Hence the aim of the study is to systematically review the association between melatonin level and periodontitis and quantitatively show the results through meta analysis .

AIM AND OBJECTIVES:

To do systematic review and meta analysis on association between melatonin and periodontitis.

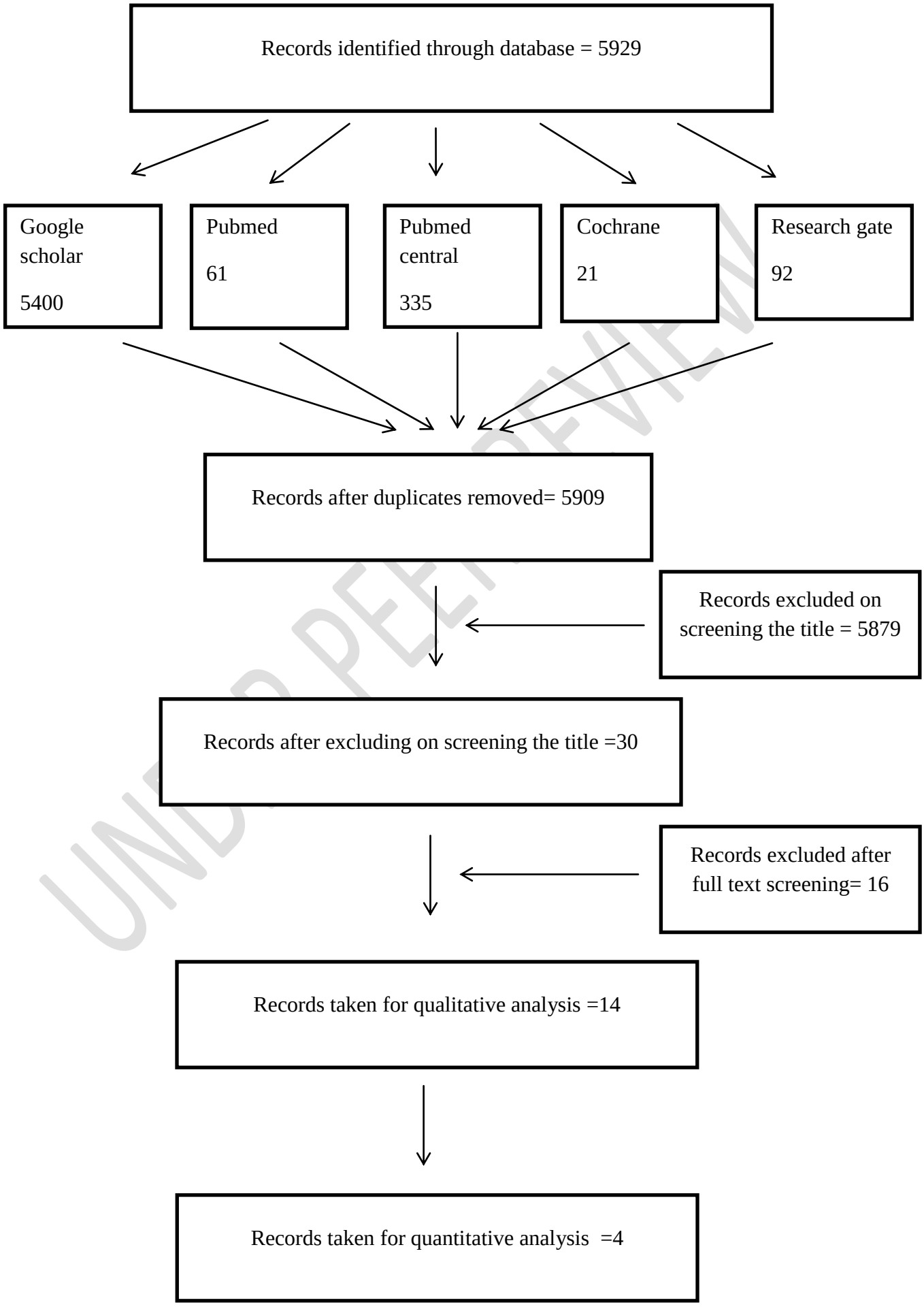
METHODS:

This is a secondary research done with an aim to find the association between periodontitis and melatonin. The search process was performed by the single author under the guidance of the guide.

The Search was undertaken with the following MeSH terms. (("Melatonin"[Mesh]) AND ("Periodontitis"[Mesh] OR "Chronic Periodontitis"[Mesh] OR "Aggressive Periodontitis"[Mesh]))

The Search of the studies is till 2020. No filters or Limits were applied in the searches on language or year of publication.

Fig 1: Flowchart of study identification, screening and inclusion.



CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW:

Inclusion criteria outlines

Types of studies

All observational and experimental studies are included for this systematic review under the following patient/population, intervention, comparison and outcomes criteria (PICO) criteria.

For observational studies

Population- periodontitis subjects

Intervention- nil

Comparison- healthy controls

Outcome- salivary/plasma/gcf melatonin levels.

For experimental studies (Randomised controlled trial)

Population- periodontitis

Intervention- melatonin

Comparison- controls

Outcome- Periodontal parameters.

Exclusion criteria

Editorial letters, reviews, in vitro studies, animal studies, descriptive studies, case reports, case series, grey literature were excluded.

Search methods for identification of studies

A comprehensive literature search of the following databases were done (Fig.1) which included studies of The Cochrane database of systematic reviews, PubMed, pubmed central, Google scholar, research gate (Until 2020) .

Selection of studies

The studies were selected by titles and abstracts based on the search strategy described previously. Then, the full texts of the potentially eligible studies were read and selected based on the inclusion criteria (PICOS criteria). Papers appearing in more than one database search were considered only once.

Assessment of risk of bias in included studies:

Each selected study was evaluated for inner methodological risk of bias.

Joanna Briggs Institute Critical Appraisal Checklist :

1. **Were the criteria for inclusion in the sample clearly defined?**
2. **Were the study subjects and the setting described in detail?**
3. **Was the exposure measured in a valid and reliable way?**
4. **Were objective, standard criteria used for measurement of the condition?**
5. **Were confounding factors identified?**
6. **Were strategies to deal with confounding factors stated?**
7. **Were the outcomes measured in a valid and reliable way?**
8. **Was appropriate statistical analysis used?**

Table 1: Assessment of risk of bias in included studies

	1	2	3	4	5	6	7	8
Gomez et al	YES	NOT CLEAR	YES	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Leila Golpasand Hagh et al	YES	NO	NOT CLEAR	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Cutando et al	NO	YES	YES	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Rashmi Srinath et al	YES	YES	NO	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Ghallab et al	YES	YES	YES	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Almugrabi et al	YES	NO	NOT CLEAR	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Thodur Malapusi Balaji et al	YES	YES	NOT CLEAR	YES	NOT APPLICABLE	NOT APPLICABLE	YES	YES
Karuna Lodhi et al	NO	YES	NOT CLEAR	NOT CLEAR	NOT APPLICABLE	NOT APPLICABLE	YES	YES

RESULTS:

This systematic review is based on the association between the melatonin levels and periodontics. In this review observational and randomized controlled trial were included.

A comprehensive literature search from various databases, Pubmed, pubmed central, Cochrane, google scholar, research gate was performed. The eligible studies were selected based on PICO criteria.

In this review 14 studies were included for systematic review (8 observational studies, Table 2. 6 Randomised controlled trial Table 3).

Based on Joanna Briggs Institute critical appraisal checklist (Table 1) four studies which have low risk of bias are included in this meta analysis.

The meta analysis was done using Review Manager 5.3 software and it showed that the mean difference between the salivary melatonin levels in healthy and periodontitis groups was statistically significant with $P<.001$. Heterogeneity between the studies is 49%. (Fig. 2)

SYSTEMATIC REVIEW

Table 2 Literature review

AUTHOR	AGE IN YEARS	YEAR	TYPE AND POPULATION	OUTCOME MEASURED	INFERENCE
Cutando	55.1 +/- 0.46	2006	Observational 37 patients with different degrees of periodontal disease	Saliva / Plasma melatonin ratio	**Significant negative correlation in saliva/plasma melatonin ratio with CPI index**
G. Gomez moreno	47.2+/- 9.1	2007	Observational Periodontitis group- 46 Control group – 26	Salivary melatonin, Plasma melatonin , CPI index	**Lower salivary and plasma melatonin than controls** . Melatonin level was decreased

					through CPI from 1-2 and increased through CPI from 2-4
Rashmi Srinath	20 – 45	2010	Observational Healthy- 15 Gingivitis- 15 Periodontitis- 15	Salivary melatonin, Gcf melatonin	**Lower salivary and Gcf melatonin in periodontitis group**. Inverse relationship exists between gingival, Russel Indices and melatonin level
Almughrabi	20-55	2013	Observational Healthy- 10 Gingivitis- 20 Chronic periodontitis- 20 Aggressive periodontitis – 20	Salivary melatonin, Gcf melatonin	**Lower salivary and gcf melatonin in aggressive periodontitis group**
Leila Golpasand Hagh	40.44+/- 6.38	2014	Observational Healthy group- 10 Gingivitis group- 10 Localised moderate periodontitis – 10 Generalised moderate periodontitis- 10 Generalised severe periodontitis- 10	Salivary melatonin	**Lower salivary melatonin in generalised severe periodontitis**. Negative correlation exists in salivary melatonin and severity of periodontal disesase
Thodur Malapuri Balaji	29.6+/-5.8 – Healthy individuals 41.18+/- 7.06 – Chronic periodontitis	2015	Observational pilot study Healthy – 5 Chronic periodontitis- 15	Saliva melatonin, plasma melatonin, Gcf melatonin	**Lower Gcf melatonin in periodontitis group and is significant** **Lower Salivary melatonin in periodontitis group but not significant**

					Higher plama melatonin in periodontitis group but not significant
Ghallab	Healthy – 26+/-2.67 Chronic periodontitis- 42.2+/-2.55 Generalised Aggressive periodontits- 26.43+/-3.62	2016	Observational Healthy – 15 Chronic periodontitis- 25 Generalised Aggressive periodontits- 25	Gcf melatonin, PI, GI, PD, CAL	**Lower gcf melatonin in generalised periodontitis group .** Significant negative correlation seen between chronic periodontitis and Gcf melatonin
Karuna Lodhi	18-65	2016	Observational pilot study Healthy- 10 Gingivitis- 10 Periodontitis- 10	Salivary melatonin	Increased Salivary melatonin in periodontitis group. Significant positive correlation exists between melatonin level and gingival index, probing depth

Table 3 Conceptual review

AUTHOR	YEAR	TYPE AND POPULATION	INTERVENTION	MELATONIN DOSAGE	OUTCOME MEASURED	INFERENCE
Marwar	2014	**Randomised controlled trial** **Total- 160** **Test- 80** **Control- 80**	**Test group- SRP and Melatonin tablet** **Control group – SRP and Placebo**	3mg daily at night for 4weeks.	**Gingival index, Periodontal disease index, community periodontal index.**	Significant difference is seen in all the indices in favour of test group
Mohammedtaghi Chitsazi	2017	**Randomised controlled trial** **Total- 60**	**Group A- SRP** **Group B- SRP and melatonin** **Group C – SRP**	2 mg a day for 4 weeks	**Gingival index, PD, CAL**	Significant improvement seen in gingival index

		Group A,B,C	**and melatonin + vitamin C**			in melatonin group after 3 and 6 months. Significant improvement in PD and CAL at 6 month in melatonin + vitamin C group No significant difference is seen in melatonin group and control group
Hesham El-Sharkawy	2018	**Randomised controlled trial** **Total- 74** **Test- 38** **Control- 38**	**Test group- SRP and melatonin** **Control- SRP and placebo**	10 mg oral melatonin capsule once daily before bedtime	**Gingival index, Plaque index, BOP, PD, CAL.**	Significant difference is seen in favour of test group
Manvel Tinto	2019	**Randomised controlled trial** **Total- 20** **Test- 10** **Control- 10**	**Test group- SRP and melatonin** **Control- SRP and placebo**	Melatonin tablets 1 mg per day at bedtime, for 30 day	**PD**	Statistical difference is seen in PD between baseline and 6 months
Anagha Marwar	2019	**Randomised controlled trial** **Total- 240** **Group A,B,C**	**Group A- SRP** **Group B- SRP + vitamin E** **Group C – SRP+ melatonin**	Tablet melatonin 3 mg daily at night for 4 weeks	Malondialdehyde , Superoxide dismutase, Glutathione peroxidase	Melatonin acts as an antioxidant in periodontitis and confer a new facet to the management of periodontitis
Mohammed Roshdy Abdel Rasoul	2019	Clinical trial – 7	Group 1 – melatonin granules Group 2 – hydroxyapetitie alloplast Group 3- melatonin + hydroxyappetite	5 mg of melatonin the form of granules	PI, GI, PD, CAL (data not available)	Statistically significant increase in alveolar bone height and radiographic bone density within the group but not between the groups.

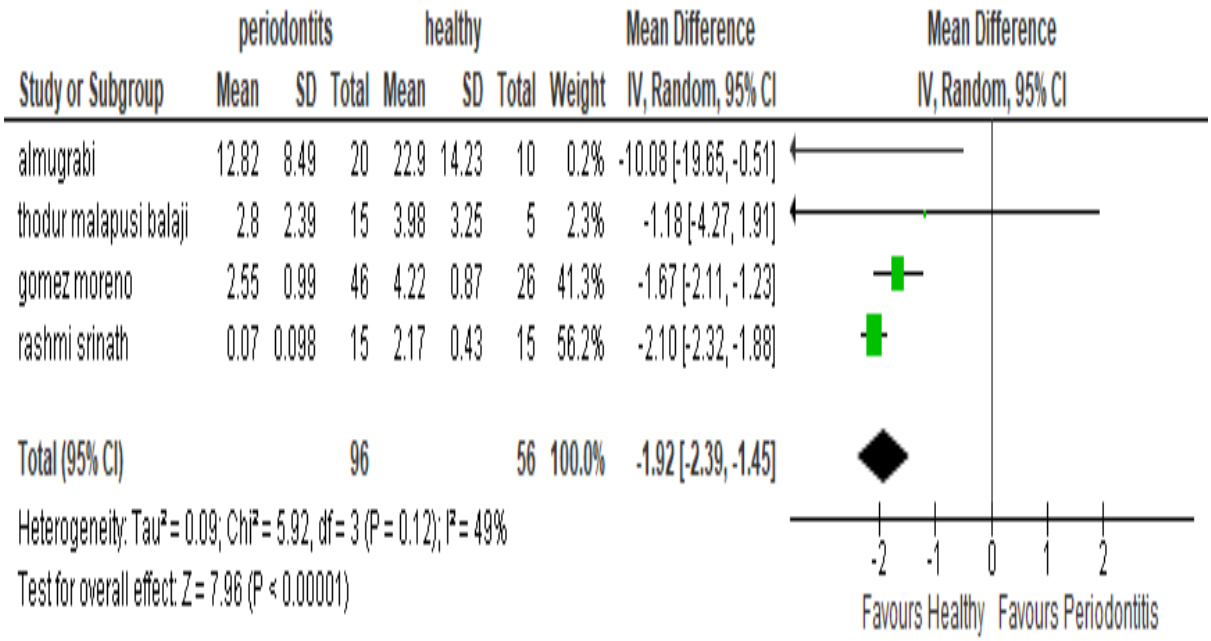


Fig 2 :Meta analysis showing the Salivaray melatonin level in healthy and Periodontitis group.

DISCUSSION:

Periodontal disease is wide spread and it is a major public health problem. According to the national oral health survey 2002-03 the prevalence of periodontal disease was 55.4 per cent in 12 years old while the prevalence peaked at 89.1 per cent in the 35-44 year age group and 79.3 per cent in 65-74 years age group.[10] Periodontitis results in progressive destruction of tooth supporting tissues (cementum, periodontal ligament, and alveolar bone) and subsequently loss of teeth. In spite of various surgical and nonsurgical therapeutic options, the global prevalence of periodontitis is still remarkably high.[11]

The levels of melatonin in the saliva are roughly one-fourth to one-third those in the general circulation (ranging from 1 to 5 pg/mL in the day and up to 50 pg/mL at night). Melatonin in the saliva is believed to be from the unbound melatonin component in the systemic circulation that passively enters the mucous/serous cells of the major salivary glands (parotid, submaxillary and sublingual glands). It is discharged from the individual acinar cells of the salivary glands due to the contraction of the myoepithelial elements of the acini.[7] Many studies have been published on showing

the association between salivary melatonin and periodontitis. This is the first systematic review and meta analysis on showing the association between the both.

In the studies done by Gomez Moreno et al [12] and Thodur Malapuri Balaji et al[13] salivary and plasma melatonin was observed in the healhy and periodontitis participants in the fomer , salivary, GCF and plasma melatonin was observed in the latter study. It was concluded that the salivary melatoin was lower in periodontitis group in both the studies and in the latter study plasma melatonin was higher in periodontitis group, however it is not significant.

Salivary melatonin was lower in periodontitis group than the controls in studies like LeilaGolpasand Hagh et al[14], Rashmi Srinath et al[15], Almugrabhi et al [16] . In the study cutando et al [17]. Saliva/plasma melatonin ratio was observed in different degrees of periodontal dsease. Significant negative correlation exists in saliva/plasma melatonin ratio with CPI index.

In the study done by Ghallab et al [18] GCF melatonin was observed with the periodontal status, significant negative correlation existed between chronic periodontitis and GCF melatonin.

Increased salivary melatonin in periodontitis and singinificant positive correlation exists between melatonin level and periodontal parameters only in the study done by Karuna Lodhi et al [19]. However it was a pilot study.

Among the experimental studies, 5 Randomised controlled trial and one clinical trial was observed. In the studies Marwar et al [20], Mohammedtaghi Chitsazi [21], Hesham El- shawkawy et al [22], Manuel Tinto [23], Anagha Marwar [24] when melatonin was given as an intervention, significant improvement in periodontal parameters were observed. In the study done by Mohammed Roshdy Abdy Rasoul et al [25], melatonin was intervened in the form of granule and significant increase in alveolar bone height was observed.

The limitation of the study is that only 5 databases were searched.

CONCLUSION:

This systematic review and meta analysis concludes that salivary melatonin level in participants with periodontitis is significantly lesser when compared to the healthy individuals. Supplementation of melatonin improves the periodontal condition.

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