Review Article

Estimation of Serum, Salivary, and Gingival Crevicular Uric Acid of Individuals With and Without Periodontal Disease: A Systematic Review and Meta-analysis

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ABSTRACT

Introduction: Uric acid (UA) levels in serum, salivary, and gingival crevicular fluid (GCF) may be associated with periodontal diseases. Hence, this study aimed to estimate the UA concentration in serum, saliva, and GCF of periodontal disease and non-periodontal disease subjects by conducting a systematic review and a meta-analysis of the reported studies. **Materials and Methods:** A review of the available literature was searched in the electronic databases of PubMed, Cochrane, Science Direct, and EBSCO for the relevant publications. All the related case–control, cross-sectional, and cohort studies reporting the UA levels in the blood, salivary, and GCF between periodontal disease patients and healthy controls were analyzed. Significant heterogeneity was observed in the studies. Hence, a continuous random-effects model was used. The findings are described in forest plots with the point estimations and 95% confidence interval (CI). A value of *P* less than 5% was considered as a significant heterogeneity test. **Results:** Of the initial 166 study titles screened, 14 reported papers were eligible for quantitative review. The subgroup analysis of serum UA revealed a mean difference of 0.299 (95% CI: 0.029–0.569, I^2=85.64%, P<0.001), indicating an increase in the UA levels in periodontal disease. However, the subgroup analysis by salivary UA demonstrated a mean difference of −0.783 (95% CI: −1.577–0.011, I^2= 94.62%, P<0.001), suggesting a lower side of the UA level in periodontal diseases. The subgroup analysis based on case–control studies showed a mean difference of 0.004 (95% CI: −0.286–0.294, I^2=84.99%, P<0.001), indicating no changes in UA levels in periodontal disease. On the contrary, cohort studies and cross-sectional studies showed a mean difference : 95% CI: −1.016, −3.272–1.241, I^2=97.84%, P<0.001 and 95%: −1.230, −4.410–1.949, I^2=97.7%, P<0.001, indicating reduction in UA levels in periodontal disease cases. **Conclusion:** The current review suggests an increase in the serum UA levels in periodontal disease than in healthy controls. Contrarily, the salivary UA levels decreased in periodontal disease patients. It is unknown why UA levels are opposite in the blood and saliva of periodontal disease patients requiring further explanation.

Keywords: *GCF, healthy, non-periodontal disease, periodontal disease, periodontitis, saliva, serum, uric acid*

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Introduction

Periodontal disease is a chronic inflammatory condition that affects 10–15% of the world's

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population. It is the most common cause of tooth loss that damages the surrounding and supporting structures of the tooth.[1-4] Clinical expressions are based on the presence or absence of inflammation, pocket depth, gingival, and bone losses.[1,2] As bacterial species evolve faster than human hosts, the immunological system that maintains commensal bacteria's ecological balance shifts to maintain homeostasis.[5] In the case of periodontal disease, pathogenesis is interceded by the inflammatory responses of the bacteria present in the dental plaque.[6] Thus, immune response and host susceptibility modified by environmental factors regulate the progression of periodontal disease.[7] Various studies have demonstrated that oxidative stress and total antioxidant capacity play a vital role in periodontal disease pathogenesis.[1,2,8-10] Any imbalance between the pro-oxidants and antioxidants results in oxidative stress.[1,2,11]

Uric acid (UA) ($C_5H_4N_4O_3$) is a heterocyclic organic compound having a molecular weight of 168 Da. It is the final product of an exogenous pool of purines and endogenous purine metabolism.[12] The standard reference value of UA among women is 1.5–6.0 mg/dL, and in men, it varies from 2.5 to 7.0 mg/dL. UA demonstrates low solubility in water, and in humans mean concentration of UA in the blood is close to the solubility limit of 6.8 mg/dL. Usually, most daily UA removal occurs through the kidneys.[13] Saliva has become a promising fluid in research and clinical diagnosis. It is regarded as an essential biomarker complementing the diagnosis of some systemic diseases.[14,15] Oxidative stress and antioxidant levels in saliva have been reported in periodontitis associated with many systemic conditions.[16-18] UA, albumin, and ascorbic acids are the main antioxidant constituents of saliva.[19] However, UA in saliva has clinical significance in monitoring oxidative stress.[20]

Oral diseases affecting the alveolar bone or teeth have increased blood UA levels.[21-23] Recent studies relate elevated UA levels to periodontitis.[21,24,25] UA contributes approximately 70–85% of the total antioxidative potential of resting and stimulated saliva from healthy and periodontally compromised subjects.[26,27] In addition, salivary UA and plasma UA concentrations are similar without any significant diurnal variation.[28] However, controversy surrounds estimating UA levels in saliva and periodontal disease. UA is comparatively less among periodontitis patients than healthy controls.[29] In contrast, Moore *et al.*[26] have reported that increased salivary concentrations of UA suggest oxidative stress and the progression of periodontal disease.

In order to acquire further knowledge of UA levels in serum, saliva, and GCF in periodontal diseases and health, there is a need to examine the published literature to ascertain its role in systemic and oral health and disease. Therefore, the current study aims to estimate the UA concentration in serum, saliva, and gingival crevicular fluid (GCF) of periodontal disease and non-periodontal disease (healthy) subjects by conducting a systematic review and a meta-analysis of the reported studies.

Materials and Methods

To achieve the objective of this systematic review, a focused research question was formulated with the following components:

(i) *Cases*: Individuals/patients with periodontal disease;
(ii) *Comparison*: Individuals without periodontal disease or healthy subjects;
(iii) *Outcome*: concentration of UA in serum or saliva or GCF.

Focused question

Does the UA levels in saliva or serum or GCF differ among the patients with periodontal disease compared with non-periodontal disease (healthy)?

Periodontal disease included both periodontitis and gingivitis as defined below:

Periodontitis: Periodontitis included a minimum of two areas of different teeth having clinical attachment level (CAL): at least two sites on different teeth with CAL ≥ 6 mm and at least one site with probing pocket depth (PPD) ≥ 4 mm[30] or a minimum of two areas of non-adjacent teeth proximal attachment loss ≥3 mm,[31] or community periodontal index (CPI) score of 4 in at least one quadrant.[32] However, in situations with no reported CAL or PPD, a radiographic alveolar bone loss was ≥ 30% of root length or ≥ 5 mm in at least two teeth.

Gingivitis included a minimum of 30% of sites with bleeding on probing or mean bleeding index = 1,[33] or at least 15 bleeding sites.[34] In some cases, gingivitis refers to unspecified gingival inflammation. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in this study in conducting systematic review and meta-analysis [Figure 1].

Literature search strategy and selection of publications

In July 2021, searches were conducted in the PubMed, Cochrane, Science Direct, and EBSCO databases to

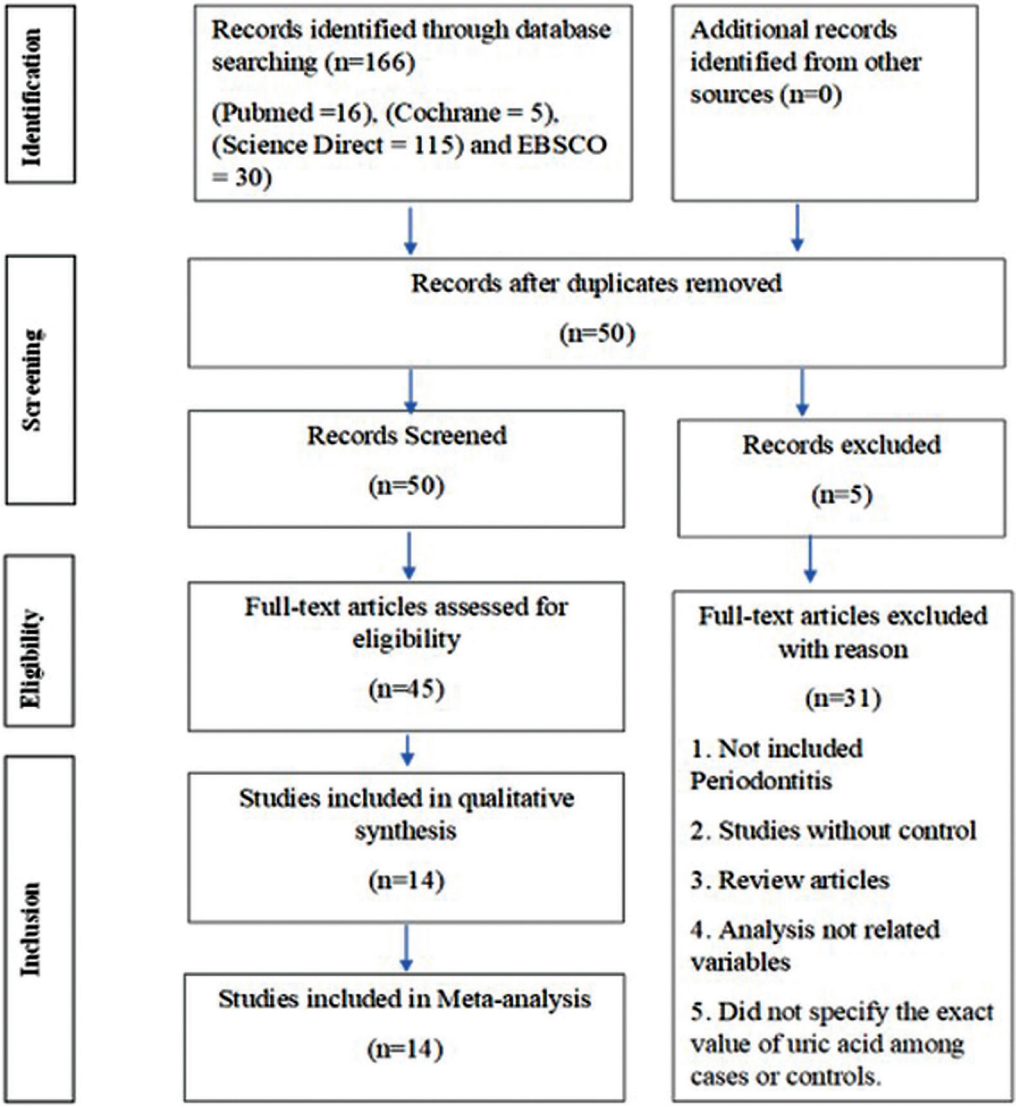

Figure 1: PRIMSA flow chart

find the most relevant papers published. The following keywords were used in the search strategy: Uric acid, periodontitis patients, non-periodontitis, serum, saliva, GCF using an advanced search strategy. A single calibrated reviewer independently selected the articles. The initial screening was performed by reading the titles and abstracts. After reading the complete text, the decision was taken if the information was insufficient.

Inclusion and exclusion criteria

The inclusion criteria were all articles identified in the database searches, filtered by "humans" but without filtering by publication date or age of subjects. In addition, studies linking oral disease to other types of systemic disease were included in the review. Literature reviews, case reports, and animal-based studies were excluded. Studies that did not address oral disease lacked a control group or examined variables other than the objective of the present review were also excluded. Moreover, publications other than the English language were translated into English and included in the study.

Data extraction

Descriptive information, including the study author, year, study design, sample, UA measuring method, comparison group, the total number of cases, mean and standard deviation values of UA in cases, total controls, mean and standard deviation values of UA in controls, and significant findings, was extracted from each study. The summary of studies and outcome measures are shown in Table 1.

Quality assessment

The quality of each study was measured on the Newcastle–Ottawa quality assessment scale for case–control, cohort, cross-sectional studies (NOS), and

Table 1: Summary of studies and outcome measures included in the meta-analysis

Study	Study design	Sample	Total cases	Mean UA cases	SD cases	Total control	Mean UA control	SD controls	Findings
Moore *et al.*[26]	Case–control	Saliva	7	255 µmol/L	89 µmol/L	28	219 µmol/L	64 µmol/L	Saliva's antioxidant capacity seems to be unaffected in individuals with periodontal disease
Shetty and Talaviya[29]	Case–control	Saliva	30	4.449 mg/dL	2.658 mg/dL	30	4.878 mg/dL	4.012 mg/dL	Uric acid of periodontitis patients comparatively less than non-periodontitis patients
Tu *et al.*[35]	Cross-sectional	Serum	10,383	9.085 mg/dL	2.79 mg/dL	18,538	8.73 mg/dL	2.025 mg/dL	MetS and the diagnosis of periodontal diseases inwomen and a weaker association in men
Mathur *et al.*[36]	Prospective cohort intervention	Saliva	10	2.43 mg/dL	0.42 mg/dL	10	5.19 mg/dL	0.8 mg/dL	Non-surgical periodontal therapy induced increased levels of salivary UA in gingivitis/ periodontitis patients
Miricescu *et al.*[40]	Case–control	Saliva	20	2.41 mg/dL	0.265 mg/dL	20	3.12 mg/dL	0.85 mg/dL	Salivary activities for UA were decreased in patients with chronic periodontitis vs. controls
Novakovic *et al.*[39]	Randomized controlled intervention	Saliva	42	198.42 µmol/L	87.73 µmol/L	21	153.95 µmol/L	41.87 µmol/L	SRP enhanced salivary UA levels compared to baseline in periodontitis patients. However, UA was not correlated with clinical periodontal parameters at baseline.
Banu *et al.*[21]	Case–control	**Serum**	40	5.32 mg/dL	0.95 mg/dL	20	4.42 mg/dL	0.68 mg/dL	Plasma UA levels were highly increased in periodontitis patients compared with control individuals
Cao *et al.*[24]	Case–control	Serum	112	402 µmol/L	95.8 µmol/L	53	364.7 µmol/L	72.4 µmol/L	In patients with IgA nephropathy, severe periodontitis was associated with a higher serum UA level than other periodontitis types

Table 1: Continued

Study	Study design	Sample	Total cases	Mean UA cases	SD cases	Total control	Mean UA control	SD controls	Findings
Fatima *et al.*[41]	Cross-sectional	Saliva	20	2.5 mg/dL	0.625 mg/dL	10	5.39 mg/dL	1.49 mg/dL	Periodontally healthy individuals without smoking habits had significantly high uric acid level in saliva as compared to smoker and non-smoker patients with periodontitis
Shetty *et al.*[36]	Case–control	Saliva	15	1.11 mg/dL	0.48 mg/dL	15	1.7 mg/dL	0.58 mg/dL	The periodontitis group exhibited comparable serum UA levels to those without periodontitis in pregnant women with preeclampsia
Shetty *et al.*[36]	Case–control	Saliva	15	1.66 mg/dL	0.55 mg/dL	15	1.57 mg/dL	0.55 mg/dL	Normotensive pregnant women with periodontal health with the periodontal disease showed nearly comparable salivary uric acid levels. However, uric acid differed significantly between preeclamptic periodontitis women and pregnant normotensive women with periodontitis
Narendra *et al.*[41]	Case–control	Serum	78	5.12 mg/dL	0.32 mg/dL	50	5.11 mg/dL	0.54 mg/dL	The UA levels in GCF and serum were both unaffected in chronic/aggressive periodontitis vs. controls
Narendra *et al.*[41]	Case–control	GCF	78	4.91 mg/dL	0.4 mg/dL	50	5.11 mg/dL	0.53 mg/dL	The UA levels in GCF and serum were both unaffected in chronic/aggressive periodontitis vs. controls
Babaei *et al.*[25]	Randomized controlled intervention	Serum	20	4.48 mg/dL	1.34 mg/dL	20	5.28 mg/dL	1.7 mg/dL	Supplement of chicory leaf extract with non-surgical periodontal therapy reduced serum UA level compared to baseline

UA=uric acid, SD=standard deviation, mg/dL=milligram per deciliter, µmol/L=micromoles per liter, MetS=metabolic syndrome, SRP=scaling and root planing, GCF=gingival crevicular fluid

Table 2: The Newcastle–Ottawa quality assessment scale

Study	Study design	Selection	Comparability	Outcome	Total*
Moore *et al.*[26]	Case–control	**	**	**	6
Shetty and Talaviya[29]	Case–control	***	**	****	9
Tu *et al.*[35]	Cross-sectional	***	**	***	8
Mathur *et al.*[36]	Prospective cohort intervention	**	**	**	6
Miricescu *et al.*[40]	Case–control	***	**	***	8
Novakovic *et al.*[39]	Randomized controlled intervention	**	**	**	6
Banu *et al.*[21]	Case–control	***	**	***	8
Cao *et al.*[24]	Case–control	**	**	**	6
Fatima *et al.*[41]	Cross-sectional	***	**	***	8
Shetty *et al.*[36]	Case–control	***	**	****	9
Shetty *et al.*[36]	Case–control	***	**	****	9
Narendra *et al.*[37]	Case–control	***	**	****	9
Narendra *et al.*[37]	Case–control	***	**	****	9
Babaei *et al.*[25]	Randomized controlled intervention	***	**	***	8

randomized controlled interventions. These consist of several items, divided into three groups: selection of study groups, comparability, and exposure or interesting findings in the groups, respectively. The stars awarded for each quality group provide a rapid visual assessment. For example, the scoring system can award 10 stars to the highest quality cross-sectional, case–control studies, and randomized controlled interventions. However, 13 stars for the assessment of cohort studies were considered [Table 2].

Subgroup analysis

Studies assessing the relationship between UA levels and periodontal disease have reported conflicting findings. So, we performed a subgroup analysis based on the studies of UA levels in saliva or serum and the study designs.

Statistical analysis

The results of studies were combined on the basis of the sample size, study design, salivary and serum UA's mean and standard deviations. The heterogeneity index (I^2) was used to assess the heterogeneity of the studies. Since significant heterogeneity was observed in the studies, a continuous random-effects model was used. The findings are described in forest plots (the point estimations and their 95% CI). A value of P less than 5% was considered as a significant heterogeneity test. All the statistical analyses were performed using OpenMeta [Analyst] software program developed by the Center for Evidence Synthesis in Health (Brown University, School of Public Health, Providence, RI, USA).

Results

Of the 166 identified study titles, 45 records were considered eligible after initial screening. After the full-text reading, 31 papers were excluded due to: (1) not reporting periodontal disease as an outcome of interest (n = 10); (2) studies without control group UA measurements (n = 10); (3) narrative reviews (n = 4); (4) analysis not related to the variables of interest (n = 5); and (5) no mention of the exact value of UA in cases and control groups (2). Hence, 14 studies were included with repeated articles separately for salivary and serum UA in the qualitative and quantitative analysis. These studies were published in different countries of the world. The study participants ranged from 7 patients in a study by Moore *et al.*[26] to 18,538 individuals in Tu *et al.*[35] Nine case–control, two cross-sectional, one prospective cohort, and two randomized controlled interventions were included in this review. The study conducted by Shetty *et al.*[36] was repeated twice due to the comparison of the salivary UA between normal individuals and periodontitis patients without pregnancy; second-time uric acid data were compared between women with and without pregnancy. Similarly, Narendra *et al.*'s study counted once for the serum UA and the GCF to compare healthy and periodontitis patients.[37] The periodontal disease criteria were based on clinical and few studies on radiographic evidence.

The quality ratings of the study showed that the total number of stars ranged from 6 to 9 for all the studies. Five studies qualified for the highest rating of nine stars. On the contrary, studies reported by Moore *et al.*,[26] Mathur *et al.*,[38] Novakovic *et al.*,[39] and Cao *et al.*[24] were assigned a score of 6. Similarly, studies conducted by Tu *et al.*,[35] Miricescu *et al.*,[40] Banu *et al.*,[21] Fatima *et al.*,[41] and Babaei *et al.*[25] were assigned an 8-star rating, as shown in Table 2.

Subgroup analysis based on serum and salivary uric acid

The subgroup analysis of serum UA revealed a mean difference of 0.299 (95% CI: 0.029–0.569, I^2=85.64%, P<0.001) [Figure 2], indicating an increase in the UA

levels in periodontal disease. However, the subgroup analysis by salivary UA demonstrated a mean difference of −0.783 (95% CI: −1.577–0.011, I^2= 94.62%, P<0.001) [Figure 3], suggesting a lower side of the UA level in periodontal diseases.

Subgroup analysis based on study designs

The subgroup analysis based on case–control studies showed a mean difference of 0.004 (95% CI: −0.286–0.294, I^2=84.99%, P<0.001) [Figure 4], suggesting no changes in UA levels in periodontal disease. On the contrary, cohort studies and cross-sectional studies showed a mean difference of 95% CI: −1.016, −3.272–1.241, I^2=97.84%, P<0.001 [Figure 5] and 95%: −1.230, −4.410–1.949, I^2=97.7%, P<0.001 [Figure 6], indicating reduction in UA levels in periodontal disease cases.

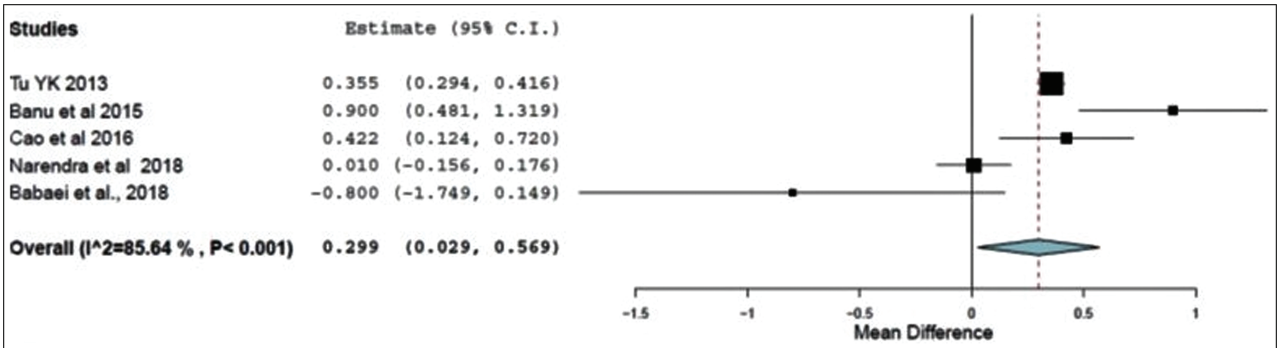

Figure 2: Subgroup analysis based on serum uric acid estimation

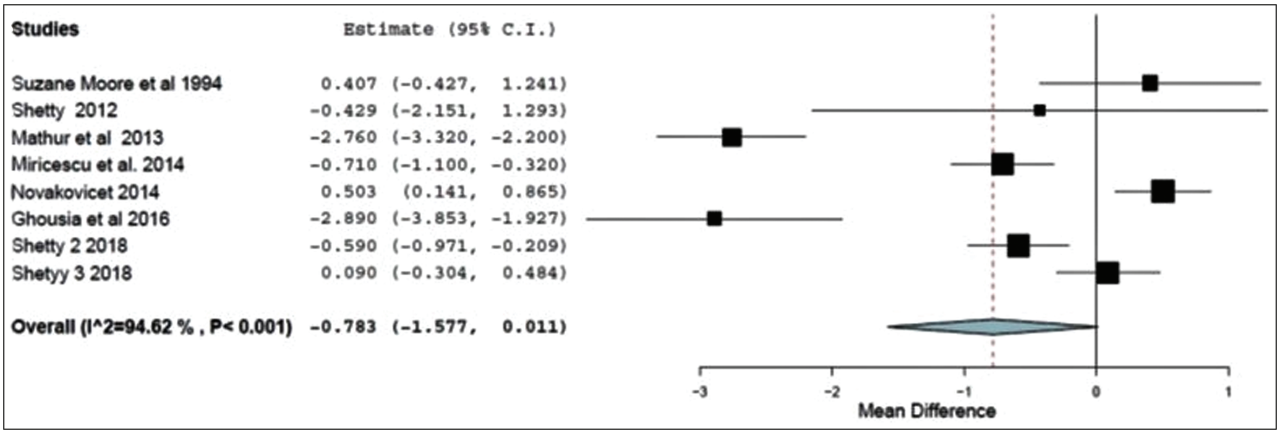

Figure 3: Subgroup analysis based on salivary uric acid estimation

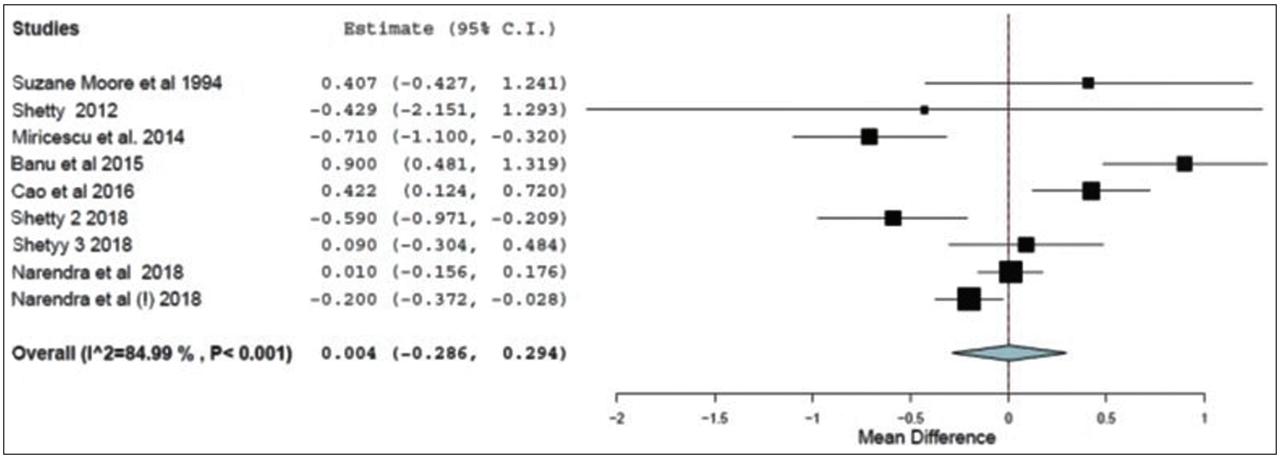

Figure 4: Subgroup analysis based on case–control studies

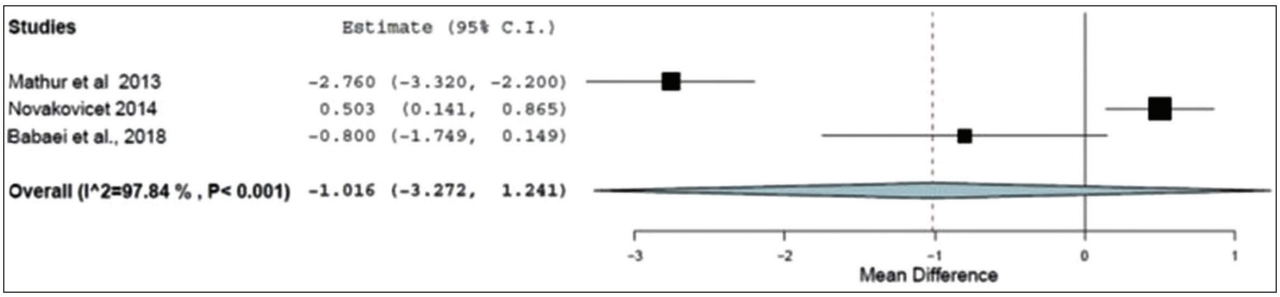

Figure 5: Subgroup analysis based on cohort studies

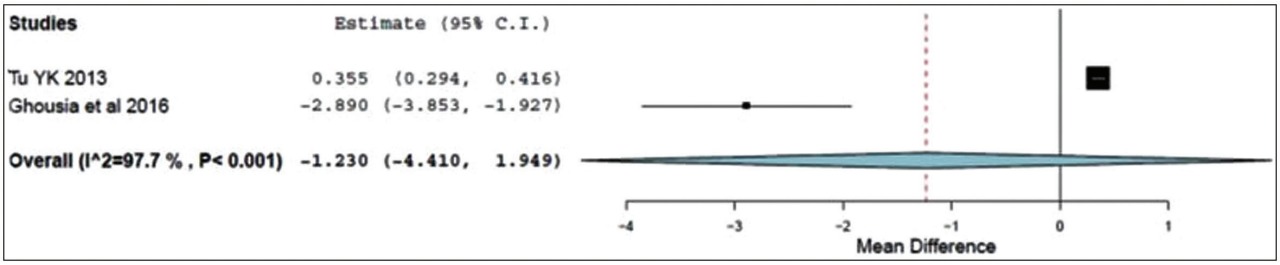

Figure 6: Subgroup analysis based on cross-sectional studies

Discussion

The study revealed contradictory findings of UA levels in serum and saliva of periodontal disease patients compared with healthy subjects, as evidenced by this meta-analysis. The UA levels in serum/plasma of the periodontal disease patients were increased compared with their healthy counterparts. Studies relating UA levels in serum/plasma with periodontal disease conditions are listed in Table 1.

Human observational studies commonly showed increased UA levels in the circulation (serum or plasma) in the presence of periodontitis with or without comorbidities.[21,24,35] Contrarily, one interventional study considered in this review found a decrease in the UA in the serum of periodontitis patients.[25] While Narendra *et al*.[37] reported no change, Tu *et al*.[35] noted a marginal reduction in serum UA levels in periodontal disease patients compared with the reference group.

These data support the notion that there is a positive connection between increased blood UA levels and periodontitis in a normouricemic condition. Notably, no research has examined the relationship between blood UA levels and periodontitis in a hyperuricemic population. In addition, no studies have been conducted to determine the impact of UA-lowering treatment on periodontal health. At the same time, the cutoff thresholds for defining UA levels in serum/plasma are arbitrary.[42]

Contradictory to the findings in serum/plasma, UA levels were decreased in the saliva of periodontitis patients in our study.[29,40,41] These inconsistent results could be attributed to the different organic origins of the serum and salivary UA. It has been hypothesized that although the UA synthesis is increased in periodontitis, the much-expanded oral biofilm may consume significantly more purine and UA through bacterial mechanisms.[43] This concept might explain why periodontitis patients had higher purine catabolism in GCF but a lower UA level than periodontally healthy controls.[44]

Of the nine studies comparing salivary UA levels between periodontitis and healthy subjects, three studies reported a decrease in salivary UA levels.[29,40,41] Mathur *et al*.[36] noted that the non-surgical periodontal treatment raised salivary UA levels in individuals with gingivitis/periodontitis.

In a case–control study, Shetty and Talaviya[29] compared the salivary UA level between periodontitis patients and healthy controls using Ramfjord index teeth. The results revealed comparatively lower UA values among periodontitis patients than the normal individuals without any significant difference. However, the study was conducted with a smaller sample size, thereby limiting the external validity of the findings.

Miricescu *et al*.[40] explored the likely relationship between salivary markers of oxidative stress and alveolar bone loss in chronic periodontitis patients and healthy controls. UA

levels were significantly decreased in patients with chronic periodontitis than in controls. Moreover, a significant negative correlation was observed between salivary UA and C-terminal telopeptide of type I collagen (CTX I) and between metalloproteinases-8 (MMP-8) and UA, suggesting alveolar bone loss. Likewise, Fatima *et al.*[41] compared the salivary UA level of healthy individuals and smokers and non-smokers with periodontitis. The study findings indicated that the patients with periodontal disease, either alone or in conjunction with a smoking habit, had decreased salivary UA levels. Interestingly, smoking did not result in additional UA depletion in periodontitis patients. However, one of the study's limitations is the smaller sample size.

In contrast to the studies that pointed out a decrease in salivary UA among periodontitis patients, some authors reported no change in UA.[26,36] Moore *et al.*[26] argued that changes in antioxidant status or levels could not detect the increased free radical generation in periodontal disease. Increased GCF production associated with gingivitis and periodontitis may potentially compensate for the local antioxidant deficiency. Additionally, Shetty and colleagues[36] reported that normotensive healthy and periodontitis pregnant women have comparable UA levels. However, a significant difference in UA was observed among pregnant women, especially between the normotensive periodontitis group and preeclamptic periodontitis group, suggesting that periodontal disease may be a risk factor for the severity, development, and possible onset of preeclampsia due to decreased antioxidant capacity or increased oxidative stress.

It has been pointed out that the antioxidant enzyme is activated in inflammatory pathways to preserve connective tissue from degradation. Therefore, antioxidant activity, especially superoxide dismutase, may be increased in gingival connective tissue to protect it from degradation without affecting its level in GCF.[45] However, only one study in our review compared the UA level in GCF of chronic and acute periodontitis patients with that of the healthy controls. The results revealed significantly higher UA levels in both periodontitis types than in healthy controls. However, acute and chronic periodontitis patients showed inconsistent UA levels in GCF and serum.[37]

It has been hypothesized that immuno-metabolic dysregulations have a critical role in exacerbating periodontitis in certain metabolic illnesses such as metabolic syndrome, diabetes, and cardiovascular disease.[46,47] Hyperuricemia is also associated with or is a risk factor for certain metabolic disorders. Periodontitis, hyperuricemia, and the cluster of metabolic disorders seem to have a complex interaction with hyperuricemia, a potentially increasing periodontal risk via the mediation of or as a consequence of these metabolic diseases.[42] In line with this, our review included studies irrespective of the underlying health conditions of the study participants that could have affected the serum and salivary UA levels.

Strength and limitations of the study

The strength of this study is the use of eminent databases for literature search, well-defined criteria for inclusion/exclusion, and extensive use of reference lists.

Since our review included most case–control and cohort studies, recall or selection bias might have affected the results and summary estimates. Additionally, the inclusion of two cross-sectional studies may be one of the limitations of the review since no cause and effect between UA levels and periodontitis could be explained. Despite best attempts to perform a comprehensive search and the absence of statistical evidence of bias, individual studies with quality issues may nevertheless be helpful.

Conclusion

Within the limitations, this systematic review with meta-analysis suggests an increase in the serum UA levels in periodontal disease cases than in healthy controls. Contrarily, the salivary UA levels decreased in periodontal disease patients. It is unknown why UA levels are opposite in blood and saliva in periodontal disease patients. Subgroup analysis based on the study type revealed varying UA levels in saliva and blood in periodontal disease patients when compared with the healthy controls. Further studies with large sample sizes with prospective study designs are needed to establish cause and effect relations between UA levels in serum or saliva and periodontal disease.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' contributions

Rabiya B. Uppin: Concepts, design, definition of intellectual content, literature search, data acquisition, manuscript preparation, manuscript editing, manuscript review. Sheeja S. Varghese: Concepts, design, definition of intellectual content, literature search, manuscript editing, manuscript review.

Ethical policy and institutional review board statement

The study proposal was registered in the research and innovation center of Riyadh Elm University (FRP/2021/426/722).

Patient declaration of consent

Not applicable.

Data availability statement

Not applicable.

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