

Levels of Interleukins in Patients with Chronic Kidney Disease and Periodontitis: A Systematic Review

Mahmud Mohammed¹, Fabiha Jesmin², Nur Karyatee Kassim^{3,4}, Siti Lailatul Akmar Zainuddin³, Muhammad Hafiz Hanafi⁵, Muhammad Imran Kamarudin⁵, Farizan Ahmad⁵, Sirajudeen K.N.S.⁶

¹Department of Conservative Dentistry & Endodontics, Delta Medical College- Dental Unit, Dhaka, Bangladesh, ²Department of Paediatric Dentistry, Delta Medical College-Dental Unit, Dhaka, Bangladesh, ³School of Dental Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, Malaysia, ⁴Chemical Pathology Department, Hospital Universiti Sains Malaysia, Kelantan, Malaysia, ⁵School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, Malaysia, ⁶Department of Basic Medical Sciences, Kulliyah of Medicine, International Islamic University Malaysia, Kuantan, Malaysia

Abstract

Aim: To systematically review the *in vivo* clinical studies available in the literature evaluating the effect of interleukin (IL) in patients with chronic kidney disease (CKD) and chronic periodontitis (CP). **Materials and Methods:** A search was initially performed using Scopus, PubMed, and Web of Science databases published from the year 2003 to 2020. Among the keywords used in the search were “periodontal diseases,” “interleukin,” “chronic kidney diseases,” and “inflammation.” After relevant articles were found, a critical assessment was made to select those that met the criteria for the systematic review. Among the inclusion criteria needed for the papers were randomized clinical trials, longitudinal clinical trials, clinical studies, no sample size limits, and only English language articles. Case reports, conference abstracts, and unpublished data were excluded for this study. **Result:** Based on the keywords, 16 of the relevant articles were listed and seven of them were selected for a systematic review. **Conclusion:** After reviewing the articles based on their results and conclusion, it can be concluded that serum IL level increased significantly in patients with CKD and CP and periodontal therapy can significantly reduce the level of serum IL. Moreover, the effect of modern periodontal therapy in CKD and CP is still unknown and inflammatory gene expression profile in patients with CKD will still need to be evaluated within different populations.

Keywords: Inflammation, Chronic Kidney Diseases, Interleukin, Periodontal Diseases

Received: 06-12-2020, **Revised:** 09-03-2021, **Accepted:** 21-02-2021, **Published:** 19-08-2021.

INTRODUCTION

Periodontitis is a chronic inflammatory disease that involves the supporting structures of teeth, including periodontal ligament, gingiva, and alveolar bone.^[1] It starts from the interaction between bacterial existence in the biofilm of the plaque and immune response of the host body. Moreover, serum inflammatory markers may increase due to poor control of periodontal disease, which may lead to systemic disease.^[2]

Various renal pathologies influence the reduction of glomerular filtration rate (GFR) to less than 60mL/min/1.73 m², which is the consequence of CKD.^[3] CKD results from the progressive and chronic destructions of nephrons, which happens over the course of a month

to a year. Cardiovascular disease, early death, and last-stage renal disease are some of the ultimate consequences of CKD. Periodontitis is considered a modifiable contributing factor for the progression of CKD.^[3]

The previous study results showed that CP was significantly more frequent among patients with CKD in comparison with healthy people. Besides, periodontal disease was relatively more severe and frequent in patients with CKD. A remarkable association was observed in which the tissue

Address for correspondence: Dr. Nur Karyatee Kassim, School of Dental Sciences, Universiti Sains Malaysia, Health Campus, Kelantan, Malaysia and Chemical Pathology Department, Hospital Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia. E-mail: karyatee@usm.my

Access this article online

Quick Response Code:



Website:
www.jioh.org

DOI:
10.4103/jioh.jioh_344_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

How to cite this article: Mohammed M, Jesmin F, Kassim NK, Zainuddin SL, Hanafi MH, Kamarudin MI, *et al.* Levels of interleukins in patients with chronic kidney disease and periodontitis: A systematic literature review. J Int Oral Health 2021;13:313-8.

level of interleukin-6 (IL-6) plays an important role in the terminal differentiation of B-lymphocytes to plasma cells. They are the predominant inflammatory cells in tissues that are involved in establishing and advancing periodontal disease and T cell proliferation and bone resorption.^[4] Further, some studies suggested continuous bacterial spreading from periodontal pockets through the bloodstream to organs including kidneys, which forms a relationship between both diseases based on biological hypotheses.^[5] Previously, study results showed that there is a noticeable impact of surgical and nonsurgical periodontal therapy on serum IL level. This serum IL had been found to be elevated and significantly expressed in patients with progressive CKD.^[6]

The PICO statement of this study inquires about the changes of different serum IL levels in patients with CKD and CP on pre- and post-periodontal treatment and the effects of IL in different populations after periodontal treatment; it also aims at identifying the potential research gaps in these studies. Hypothetically, this study aims at systematically reviewing the available *in vivo* clinical studies in the literature measuring the serum IL levels in patients with CKD and CP to find the answer to our (PICO) question by assessing and comparing the different IL levels in patients with CKD and CP in a different population, as well as the measurement methods and potential effects of periodontal therapy on serum IL levels.

MATERIALS AND METHODS

Preferred Reporting Items for Systemic Reviews and Metal-Analyses (PRISMA) 2009 guidelines (<http://www.prismastatement.org/>) were followed for the preparation of this manuscript. The literature search was conducted independently in three different databases, PubMed (end of searching on May 18, 2020), Web of Science (end of searching on December 29, 2020), and Scopus (end of searching on May 28, 2020), by two different authors (MM and FJ). The search terms used were “periodontal diseases,” “periodontitis,” “chronic periodontitis,” “juvenile periodontitis,” “gingivitis,” “acute necrotizing ulcerative gingivitis,” “aggressive periodontitis,” “localized periodontitis,” “localized aggressive periodontitis,” “interleukin,” “IL,” “serum antigen,” “serum marker,” “chronic kidney diseases,” “chronic renal diseases,” “renal failure,” “kidney failure,” “nephritis,” “renal insufficiency,” and “inflammation.” There are two main authors (MM and FJ) who had independently evaluated the selected articles according to their titles and abstracts. By checking the cross-references and identical studies, it was hoped that this could prevent missing any related articles during the initial search; thus, references of the selected studies were also analyzed carefully For eligibility, full-text

studies were assessed alongside the qualitative synthesis that was carried out. All records were screened based on the inclusion and exclusion criteria.

It was not appropriate to apply statistical methods to estimate the overall risks of bias for the case-control and cohort studies due to the high level of heterogeneity in periodontal disease, CKD, and adverse IL outcome definitions across studies. However, Modified Downs and Black checklists were implemented to evaluate the risk of bias.^[7]

Searching criteria

The literature search covered papers published from 2003 to 2020. Among the criteria used for study selection were as follows:

- (1) They were comparative studies (i.e. case-control, cross-sectional, cohort, or nonrandomized controlled studies or randomized controlled trials) of CP and CKD;
- (2) At least one of the several clinical periodontal indexes defines periodontal disease; and
- (3) Identified outcomes were the effects of interleukin in CKD and CP.

Any unpublished data, conference abstracts, and case reports were excluded from the study. The same authors (MM and FJ) assessed the risk of bias for the selected studies. There is a total of five principal segments to evaluate in each study. The segments included internal validity confounding, internal validity bias, external validity, and power. One point was given for each study if any of the criteria were fulfilled. Alternatively, 0 points were given to studies that did not fulfil the respective criteria. An additional assessment was carried out to evaluate the clinically significant effects of the study.

Observational and considerable parameters

Out of 27 points, articles that scored less than 17 recommended the presence of limitations in methodology. According to the PICOS guideline, all the data were extracted from each study, which included the population involved, type of methods used for measuring the IL-1, IL-6, and IL-8 level, location of the study, effects of periodontal therapy, and results within general outcomes [Table 1].

Two reviewers (MM and FJ) extracted all the data sets independently. All the disharmony was resolved by discussing with the third reviewer. In addition to that, advice was also taken from the third reviewer (NKK). The whole process was carried out unblinded. Hand searching was also performed in the library to check the publication bias or selective studies.

The primary outcome measure for assessing the effects of IL was the level of IL-6 and IL-8 in patients with CKD and CP. The secondary outcome was the prognosis of periodontal therapy and its effects on serum IL-6 and

Table 1: Summary of extracted data from selected study

No.	Authors, year of publication	Population type, sample size, age, and sex	Types of IL	Methods/tools	Effect and types of periodontal therapy	Results
1	(Choudhury, 2010) ^[8]	<i>Study location:</i> USA <i>Sample size:</i> 140 <i>Age group:</i> not mentioned <i>Sex:</i> common	IL-6	The IL-6 level was analyzed using ELISA method. Analytical sensitivities for IL-6 assay were 2.0 pg/ml and <0.3 mg/L, respectively, and the within-runs variation was <1 %.	The effect and types of periodontal therapy were not mentioned	Patients with CKD and severe periodontitis revealed a higher IL-6 in comparison with periodontally healthy controls
2	(Dağ <i>et al.</i> , 2010) ^[12]	<i>Study location:</i> Turkey <i>Sample size:</i> 86 <i>Age group:</i> 18–72 years <i>Sex:</i> not mentioned	IL-8	IL-8 in the samples was determined, using IMMULITE 1000 Automated Immunoassay System.	The effect and types of periodontal therapy were not mentioned	The gingival crevicular fluid from patients undergoing dialysis contains significantly higher levels of TNF and IL-8 than those from healthy controls.
3	(Vilela <i>et al.</i> , 2011) ^[6]	<i>Study location:</i> Brazil <i>Sample size:</i> 112 <i>Age group:</i> 53.17±12.00 <i>Sex:</i> not mentioned	IL-6	The concentration of IL-6 was evaluated using the Human IL-6 ELISA Kit II BD OptEIA (BD Biosciences, CA, USA).	<i>Type of periodontal therapy:</i> Nonsurgical periodontal therapy <i>Outcome:</i> Periodontal treatment significantly reduced the serum IL-6 level in patients with CP and CKD. <i>Follow-up duration:</i> 15, 30, 60, and 90 days	Patients with CP and CKD revealed a higher IL-6 in comparison with healthy controls ($P = 0.04$). Periodontal treatment significantly reduced the serum IL-6 level in patients with CP and CKD.
4	(Braosi <i>et al.</i> , 2012) ^[13]	<i>Study location:</i> Brazil <i>Sample size:</i> 246 <i>Age group:</i> 20–77 years <i>Sex:</i> equal male and female	IL-1	The samples were analyzed by PCR-RFLP. IL-1 gene transcript levels from gingival tissues were analyzed by real-time PCR	The effect and types of periodontal therapy were not mentioned	Periodontal disease affects the systemic inflammation of patients with CKD. Besides, higher levels of IL-1 gene transcript were found in patients with CP.
5	(Solomon <i>et al.</i> , 2013) ^[9]	<i>Study location:</i> Romania <i>Sample size:</i> 56 <i>Age group:</i> >18 years <i>Sex:</i> 32 males and 24 females	IL-6	The samples were analyzed using ELISA high-sensitivity sandwich method.	<i>Type of periodontal therapy:</i> Nonsurgical periodontal therapy <i>Outcome:</i> The level of IL-6 levels is markedly reduced after the periodontal treatment. <i>Follow-up duration:</i> 15, 30, 60, and 90 days	Significantly higher serum IL-6 ($P = 0.04$) reported in patients with CP and CKD compared with patients with CP without any systemic diseases.
6	(Wehmeyer <i>et al.</i> , 2013) ^[10]	<i>Study location:</i> USA <i>Sample size:</i> 51 <i>Age group:</i> 52.7 ± 10.6; 54.1 ± 9.0 <i>Sex:</i> 33 males and 18 females	IL-6	IL-6 was measured by high-sensitivity enzyme-linked immunosorbent assay (R&D Systems) and was read out using a SpectraMax M2 from Molecular Devices.	<i>Type of periodontal therapy:</i> Nonsurgical periodontal therapy <i>Outcome:</i> Periodontal therapy in patients undergoing dialysis did not produce any significant impact on serum IL level. <i>Follow-up duration:</i>	There is no significant discrepancy between IL-6 level at any time when adjusted for body mass index, diabetic status, and plaque index.
7	(Guo and Lin, 2017) ^[11]	<i>Study location:</i> China <i>Sample size:</i> 83 <i>Age group:</i> 39–75 years <i>Sex:</i> 45 males and 38 females	IL-6	IL-6 was tested by ELISA kits (MyBioSource, USA)	<i>Type of periodontal therapy:</i> Nonsurgical periodontal therapy <i>Outcome:</i> After periodontal treatment, serum IL-6 levels of patients with CP and CKD were significantly decreased ($P < 0.05$). <i>Follow-up duration:</i> Six weeks	After treatment, serum IL-6 levels of patients with CP and CKD were significantly decreased ($P < 0.05$).

IL-8. We also sought to pull out information related to the effectiveness of the interventions.

RESULTS

The selection procedure was performed by searching separate databases according to PRISMA 2009 guidelines, and it was given in a flow diagram [Figure 1]. Overall, 46 abstracts were recruited out of 95 articles that were found through the databases. Finally, seven studies were selected for the review. Thirty articles were rejected as they were irrelevant to the keywords, case reports, pilot studies, and incomplete data. Among the seven included studies, five articles had measured serum IL-6 in patients with CKD and CP.^[6,8-11] The remaining two studies measured serum IL-8 in patients with CKD and CP^[12] and serum IL-1 gene transcription in patients with CKD and CP.^[13] Out of seven studies, only four studies showed the effects of periodontal therapy on serum IL levels.^[6,9-11] Nonsurgical periodontal therapy was conducted in all four studies, which included scaling, deep curettage, root planning, and oral hygiene instruction. Out of the four studies,

only one study reported no improvement in serum IL level after periodontal therapy. The articles were all written in English with a total of 46 papers from different databases; seven papers fulfilled the inclusion criteria. We did not find any papers by manual search. Five of the seven studies that scored 17 and above were categorized as high quality.^[8-10,12,13] Besides, one study that scored 14 was categorized as fair quality.^[11] Finally, one study that scored 12 was categorized as low quality [Table 2].^[6] The pivot chart for the risk of bias assessment is displayed in Figure 2.

Limited studies were found to assess the underlying mechanism of inflammatory gene expression of the IL in patients with pre-dialysis CKD and CP. Six of the seven studies reported a significant increase in serum IL-6 and IL-8 levels in patients with CKD and CP^[6,8,9,11-13]; however, one study that was carried out in the United States reported negative results for increased serum IL levels in patients with CKD and CP.^[10] All of the included studies assessed the different types of serum IL in patients with CKD and CP. However, only four studies mentioned the impact of periodontal therapy on the reduction of serum IL levels. The most common method for estimating the serum IL level was the ELISA technique. Three studies mentioned that periodontal therapy significantly reduces the serum IL levels in patients with CKD and CP.^[6,9,11]

DISCUSSION

With the aim of reducing the possibility of missing any important study that is relevant to our search, the inclusion criteria were strongly maintained. Publication year limitations were present in this study. Moreover, the search was also limited to the English language without any sample size restriction. Despite all the measures, in total, seven potential studies were eligible for the review. Some systemic conditions such as diabetes mellitus, cardiovascular disease, and CKD are connected to periodontitis due to its inflammation-linked pathogenesis with periodontitis.^[14]

Because of the relationship with the systemic inflammatory response, chronic periodontitis can influence the progression of CKD. Growing evidence showed that CP might become an additional factor for the progression of CKD.^[3] It is believed that progressive

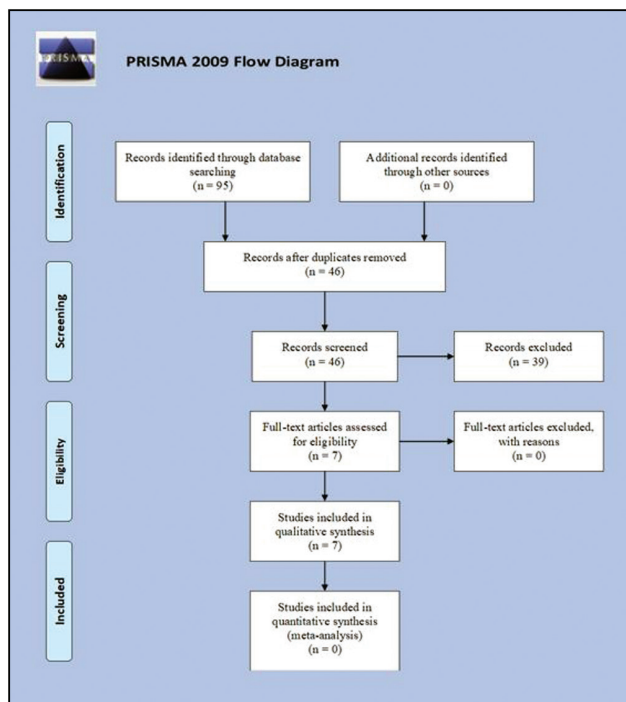


Figure 1: Prisma flow diagram

Table 2: Downs and black checklist

	Choudhury, 2010	Dağ <i>et al.</i> , 2010	Vilela <i>et al.</i> , 2011	Braosi <i>et al.</i> , 2012	Solomon <i>et al.</i> , 2013	Wehmeyer <i>et al.</i> , 2013	Guo and Lin, 2017
Reporting	7	6	5	9	8	6	7
External validity	3	3	2	3	3	3	1
Internal validity	7	10	4	6	7	7	5
Power	1	1	1	0	1	1	1
Total score	18	20	12	18	19	17	14

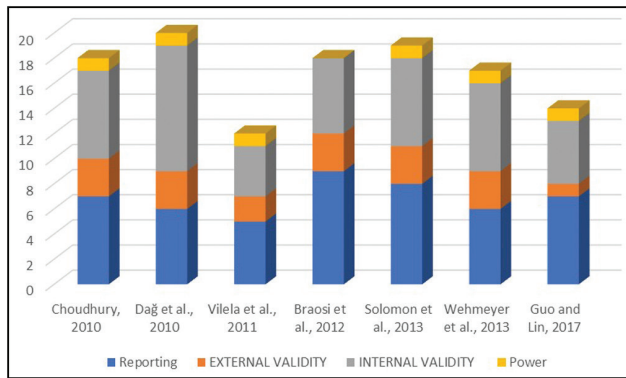


Figure 2: Pivot chart for risk of bias assessment

systemic inflammatory burden is due to the infection of periodontal pathogens, and it increases cardiovascular morbidity and mortality rates in patients with CKD.^[14] Previous studies have reported that severe periodontal destruction is significant in patients with CKD than in the general population.^[15] Besides, CKD samples were marked by some deep-rooted risk factors of periodontitis such as diabetes and poor oral hygiene.^[16,17]

Moreover, CKD can affect oral structures such as oral mucosa, periodontium, tongue, and salivary glands, resulting in an adverse effect on the oral health status.^[15] Moreover, evidence has shown that there are elevated serum levels of C reactive protein (CRP) and inflammatory cytokines such as different types of IL, which were observed in patients with long-term kidney disease and chronic periodontitis.^[12] There is a strong connection between the IL with the progression and pathogenesis of CKD and periodontitis.^[8] Among the selected studies, we found that five out of seven studies were conducted on IL-6,^[6,8-11] One study was conducted on IL-8 and one on IL-1.^[12,13] All studies evaluated the effects of IL on patients with CKD and CP. Besides, most of the studies found that patients with CKD and CP had increased serum IL 6 and IL8, which decreased after performing the nonsurgical periodontal therapy. These results clearly indicate the relationship between CKD and CP and the impact of nonsurgical periodontal therapy on the serum IL level of patients with CKD. Moreover, results of one study revealed that there was no significant difference observed within serum IL levels after performing the periodontal therapy in patients with CKD and CP.^[10] In this current study, we have systematically investigated the role of IL and its effect on systemic inflammation in patients with CKD and CP.

However, the outcome measure and the sample population were not the same. Most of the studies were carried out in a developed country,^[8-10,12] and only two studies were carried out in a developing country.^[6,13] The oral health status is different according to the geographical perspective. The result of these studies is not enough to determine the effects of IL in patients with CKD and CP all over the

world. As we know, the oral health conditions among people in different parts of the world are not the same and there may be a different effect of the serum IL on a different population. Moreover, the immune system is also different so the overall effects of IL will not be the same among the population. Hence, the role of periodontal therapy and IL level in patients with CKD still needs further investigation and evaluation.

Among the seven selected studies, only two studies measured the IL-6 level before and after periodontal therapy and mentioned that periodontal therapy decreased the IL-6 levels in patients with CKD and CP.^[6,9,11] Only one study evaluated the IL-1 gene transcription with real-time PCR in patients with CKD and CP.^[13] The study concluded that higher levels of gene transcription were noted in the same IL-1 of patients with CP in comparison with patients with CKD. It is evident in the majority of the studies that systemic inflammation may be improved by the effective management of periodontitis. It may also slow down the degree of progression of renal disease.^[6,9,13] Although periodontal management has been shown to improve the CKD progression,^[6] little is known regarding fundamental cellular and molecular mechanisms after periodontal management in patients with CKD, especially changes in the serum inflammatory markers and the involvement of inflammatory gene expression. Hence, it is essential to fill this gap. Therefore, future studies need to be carried out to understand the mechanism by analyzing the changes in both inflammatory biomarkers and inflammatory gene expression profile both before and after periodontal management in patients with CKD. Apart from that, an association between a polymorphism in the cytokine IL-1 gene cluster and CKD with CP in the different population also needs to be clarified.

Only seven full-text articles were able to be analyzed, making this the limitation of this review. In addition to that, the meta-analysis could not be performed as it lacked homogenous study results.

CONCLUSION

This systematic review of the literature shows that most studies indicate a significant increase in serum IL-6 and IL-8 levels in patients with CKD and CP; a few mentioned that periodontal treatment can be an effective way of reducing the serum IL level to stop further CKD progression. However, there are insufficient studies on the effects of IL in patients with CKD and CP; further research is needed to assess the effects of IL and its pathogenesis on patients with CKD and CP. Moreover, the effects of modern periodontal therapy are not yet known, and its effects on the expression profile of IL and inflammatory genes still need to be evaluated within different populations in patients with CKD.

Acknowledgment

Not applicable.

Financial support and sponsorship

This research was funded by the Fundamental Research Grant Scheme (FRGS/1/2019 203/PPSG/6171232), Ministry of Education, Malaysia.

Conflict of interest

The authors declare no potential conflict of interest for this article.

Author contributions

MM: data curation, formal analysis, investigation, resources, and writing—review and editing. *FJ*: data curation, resources, validation, visualization, and writing—review and editing. *NKK*: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, and editing. *MHH*: conceptualization, data curation, formal analysis, investigation, methodology, project administration, resources, supervision, and editing. *SLAZ*: formal analysis, methodology, resources, validation, supervision, visualization, and editing. *MIK*: resources, validation, visualization, supervision, and editing. *KNSS*: resources, validation, visualization, supervision, and editing. *FA*: resources, validation, visualization, supervision, and editing. All the authors approved the final version of the article for publication.

Ethical policy and institutional review board statement

Not applicable.

Patient declaration of consent

Not applicable.

Data availability statement

The data set used in the current study is available on request from the corresponding author.

REFERENCES

- Hajishengallis G. Periodontitis: From microbial immune subversion to systemic inflammation. *Nat Rev Immunol* 2015;15:30-44.

- Machado V, Botelho J, Lopes J, Patrão M, Alves R, Chambrone L, *et al.* Periodontitis impact in interleukin-6 serum levels in solid organ transplanted patients: A systematic review and meta-analysis. *Diagnostics* 2020;10:184.
- Fisher MA, Taylor GW, Shelton BJ, Jamerson KA, Rahman M, Ojo AO, *et al.* Periodontal disease and other nontraditional risk factors for CKD. *Am J Kidney Dis* 2008;51:45-52.
- Su H, Lei CT, Zhang C. Interleukin-6 signaling pathway and its role in kidney disease: An update. *Front Immunol* 2017;8:405.
- Deschamps-Lenhardt S, Martin-Cabezas R, Hannedouche T, Huck O. Association between periodontitis and chronic kidney disease: Systematic review and meta-analysis. *Oral Dis* 2019;25:385-402.
- Vilela EM, Bastos JA, Fernandes N, Ferreira AP, Chaoubah A, Bastos MG. Treatment of chronic periodontitis decreases serum prohepcidin levels in patients with chronic kidney disease. *Clinics (Sao Paulo)* 2011;66:657-62.
- Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* 1998;52:377-84.
- Choudhury ES. Periodontal infections, inflammatory markers in chronic kidney disease. 2010 SoDM Masters Theses. 177.
- Solomon CS, Rudnic I, Silvia I. The effects of periodontal therapy on biochemical inflammatory markers on renal dysfunction patients. *Rom J Oral Rehabil* 2013;5:71-6.
- Wehmeyer MM, Kshirsagar AV, Barros SP, Beck JD, Moss KL, Preisser JS, *et al.* A randomized controlled trial of intensive periodontal therapy on metabolic and inflammatory markers in patients with ESRD: Results of an exploratory study. *Am J Kidney Dis* 2013;61:450-8.
- Guo N, Lin G. Effects of nonsurgical periodontal therapy on serum inflammatory factor levels in patients with chronic kidney disease and periodontitis. *Biomed Res* 2017;28:3899-902.
- Dağ A, Firat ET, Kadiroğlu AK, Kale E, Yilmaz ME. Significance of elevated gingival crevicular fluid tumor necrosis factor-alpha and interleukin-8 levels in chronic hemodialysis patients with periodontal disease. *J Periodontol Res* 2010;45:445-50.
- Braosi AP, de Souza CM, Luczynsyn SM, Dirschnabel AJ, Claudino M, Olandoski M, *et al.* Analysis of IL1 gene polymorphisms and transcript levels in periodontal and chronic kidney disease. *Cytokine* 2012;60:76-82.
- Hasturk H, Kantarci A. Activation and resolution of periodontal inflammation and its systemic impact. *Periodontol* 2000 2015;69:255-73.
- Borawski J, Wilczyńska-Borawska M, Stokowska W, Myśliwiec M. The periodontal status of pre-dialysis chronic kidney disease and maintenance dialysis patients. *Nephrol Dial Transplant* 2007;22:457-64.
- Chen LP, Chiang CK, Chan CP, Hung KY, Huang CS. Does periodontitis reflect inflammation and malnutrition status in hemodialysis patients? *Am J Kidney Dis* 2006;47:815-22.
- Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S. Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 2001;134:629-36.