

Prevalence of Periodontitis and Effect of Non-Surgical Periodontal Therapy on CRP and Kidney Function Tests in Patients with Chronic Kidney Disease.

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Abstract:

Context: Periodontitis and Chronic Kidney Disease (CKD) together form the most challenging health issues in both the developing and developed countries. Non-surgical periodontal therapy seems to have many systemic benefits. Not many Indian studies have looked at the effect of NSPT on subjects with CKD.

Aims: To see if i) there is higher prevalence of periodontitis in patients with CKD and ii) NSPT decreases inflammatory burden and improves kidney functions in these patients.

Design: A case-control study involving 200 subjects (150 cases and 50 controls).

Materials and Methods: All subjects having chronic generalized periodontitis had serum C-RP, serum urea and eGFR measured before and after NSPT.

Results: The prevalence and severity of periodontitis is found to be higher in CKD patients as compared to controls. NSPT resulted in significant decrease in serum CRP values and significant increase in eGFR as calculated by MDRD study equation. No significant effect was seen on serum urea levels.

Conclusions: It is important to look out for periodontal infections in CKD patients. NSPT may benefit the patient by decreasing the inflammatory burden and improving kidney function.

Keywords: Periodontitis, Chronic Kidney Disease, Non surgical periodontal therapy, eGFR, C-Reactive Protein

I. Introduction

Periodontal diseases have historically been considered the most important global oral health burdens and continue to be the most common adverse dental condition seen in the human population. Chronic Kidney Disease (CKD) and its concomitant sequelae represent a major challenge to the medical world. These two diseases together pose the most challenging health issues both in developed and developing countries.

Periodontitis is defined as "an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession or both" [1]. Chronic Kidney Disease (CKD) is also known as chronic renal disease and is characterized by a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function may be unspecific and might include feeling generally unwell and experiencing a reduced appetite. Often, the disease remains undiagnosed and comes to light as a result of screening of people known to be at risk of kidney problems, such as those with high blood pressure or diabetes and those with a blood relative with CKD.

According to the 2010 Global Burden of Disease study, chronic kidney disease was ranked 27th in the list of causes of total number of deaths worldwide in 1990, but rose to 18th in 2010. About 10% of the population worldwide is affected by CKD. More than 2 million people around the world currently receive treatment with dialysis or a kidney transplant to stay alive but this may only represent 10% of people who actually need treatment to live. It is estimated that number of cases of kidney failure will increase disproportionately in developing countries, such as China and India, where the number of elderly people are increasing [2]. Globally, in more than a 100 countries (with a combined population >1 billion) more than a million people die annually from untreated kidney failure for lack of medical and financial resources [3]. Data suggests that in USA alone, CKD continues to increase with more than 20 million affected individuals, many of whom are undiagnosed [4]. This figure would be much higher in the poor and developing countries of the world where the under-privileged do not have access to even the basic medical amenities. The prevalence of CKD in India was observed to be 17.2% with ~6% having CKD stage 3 or worse [5]. CKD is a global health concern and a threat that is looming large in front of the human population and the under-privileged in the developing countries are reeling under the tremendous emotional, psychological, economical strain imposed by the disease. The burden of CKD in terms of medical costs and shortened healthy life is onerous and the affected individuals have markedly increased risk

of End-Stage Renal Disease (ESRD), Cardiovascular Disease (CVD) and premature death. In a vast and developing country like India, CKD is a challenge which the country is simply not equipped to handle. Many studies in the past have tried to figure out if periodontitis may contribute to chronic systemic diseases. Periodontitis is known to be associated with cardiovascular diseases, stroke, diabetes, metabolic syndrome, pre-term labor, low-birth weight, etc [6]. In the past two decades, studies have been focusing on many more such systemic conditions, with the association between periodontitis and CKD being one such under consideration. Review of literature indicates that there are conflicting opinions on the association between periodontitis and CKD with a number of studies finding an association between the two diseases [7-15] and a small number of studies also indicating otherwise [16-19].

Even though the incidence of CKD in India is alarming, the number of Indian studies examining this association is miniscule. Periodontitis is a treatable condition. Non-surgical periodontal treatment (NSPT), which includes scaling and root planing, is the gold standard of non-surgical procedures for management of chronic periodontitis. Studies have shown that NSPT can reduce inflammatory burden and improve endothelial function in patients with chronic periodontitis [20-23]. The aim of this study was to see if i) there is higher prevalence of periodontitis in patients with CKD and ii) NSPT decreases inflammatory burden and improves kidney functions in these patients.

II. Materials And Methods

The present study was carried out in the Department of Biochemistry and Department of Periodontics, MGV's KBH Dental College and Hospital, Nasik, NDMVP'S Medical College, Nasik and Supreme Kidney Care, Om Chambers, Nasik.

The protocol for this study was approved by the Institutional Ethics Committee of MGV's KBH Dental College and Hospital, Nasik and the Human Ethics Committee at UDIRT, Maharashtra University of Health Sciences, Nasik. (MUHS/UDIRT/138/2012) Prior to enrolment in the study, candidates who fulfilled the inclusion criteria were given detailed oral information about the study and invited to participate. A Patient Information Sheet (PIS) was handed over to them and written informed consent obtained.

It was decided to take a sample size of 50 subjects in each group and a similar number of controls. 150 patients of age ≥ 18 years with pre-diagnosed CKD and 50 controls were included in the study. The subjects were enrolled from NDMVP's Medical College, Nasik and Supreme Kidney Care, Nasik between 1st Jan 2013 and 10th Aug 2013.

CKD is classified into five stages as per K/DOQI guidelines (Table 1) based on Glomerular Filtration Rate (GFR). The normal range of GFR is 100-130 ml/min/1.73m².

Table 1: Stages of CKD [24]

Stage	Description	GFR (ml/min/1.73m ²)
1	Slightly diminished function, kidney damage with normal or relatively high GFR	≥ 90
2	Mild decrease in kidney function	60-89
3	Moderate decrease in kidney function	30-59
4	Severe decrease in kidney function (Preparation for renal replacement therapy)	15-29
5	Established Kidney Failure (Permanent renal replacement therapy)	<15

Inclusion Criteria:

I: Study group subjects:

- Patients with confirmed diagnosis of CKD of any cause for at least 6 months.
- Having ≥ 14 teeth in mouth.

II: Controls:

Controls included were the healthy persons (friends/relatives) accompanying the CKD patients to the OPD. These volunteers had

- ≥ 14 teeth in mouth.
- No previous diagnosis of CKD.

Exclusion Criteria:

Both controls and study group subjects were excluded if they

- had undergone anti-microbial/ anti-inflammatory therapy in the last 6 weeks.
- used steroidal or immunosuppressive drugs, were on statins or iron-replacement therapies.
- had undergone periodontal treatment in the last 6 months.
- used mouth –washes like chlorhexidine, etc.
- smoke or consume alcohol.
- are pregnant/lactating women or women on hormone-replacement therapy.

- have had acute inflammatory illnesses, hospitalization for cardiac or infection-related morbidity within 6 weeks before study, severe comorbid complications, previous kidney transplantation or are on experimental drug protocols.

Table 2: Distribution of subjects in the study.

Sr No.	Groups for study	No. of subjects
1.	Healthy Controls	50
2.	Patients with CKD	
	Stage I & II	50
	Stage III & IV	50
	Stage V	50

Dental Examination

All subjects enrolled in the study (Table 2) underwent a complete periodontal examination. The full mouth periodontal examination (6 sites/tooth: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, disto-lingual) was performed by a single examiner using UNC 15 probe of circular cross-section. History of hygiene habits like method of cleaning (finger, tooth-brush, datoon etc.), use of agents (powder, paste, mishri, etc.) was recorded. Habits like smoking, chewing ghutka, paan, tobacco, etc which adversely affect the periodontium were entered. Previous dental treatments and other oral parameters like redness, halitosis, pus discharge, presence of stains, plaque, calculus, bleeding on probing, etc were recorded. All patients were given advice about importance of oral hygiene and maintaining good oral health. The following parameters were assessed:

1. Periodontal status by Extent and Severity Index [25]
2. Mean Probing Pocket Depth (PPD)
3. Clinical Attachment Loss (CAL)
4. Bleeding on Probing (BOP).
5. Gingival Index (Loe and Silness, 1963) [25]
6. Plaque Index (Silness and Loe, 1964) [25]

PPD was determined by measuring the distance from the free gingival margin to the base of the pocket using a probe.

CAL was determined by measuring the distance between the cemento-enamel junction and the most apical part of the periodontal pocket.

BOP indicates the presence or absence of bleeding after probing the pocket.

2ml blood was collected by venipuncture from the median cubital vein from each subject in plain bulb from during their respective OPD/dialysis visit. Sample was allowed to clot at room temperature before centrifugation to collect serum. Following tests were performed:

1. Serum C-Reactive Protein Estimation (Immunoturbidometric Method) using Turbilyte CRP kit from Tulip Diagnostics (P) Ltd., Goa, India.

2. Kidney Function Tests:

- a. Serum Urea estimation (Urease method using kits from Accurex Biomedical Pvt. Ltd., India)
- b. Serum Creatinine estimation. (Modified Jaffe's Method using Kit from Yucca diagnostics, India)
- c. Serum creatinine values were incorporated in the MDRD study equation to calculate eGFR which was used to confirm the CKD staging of the patient.

The MDRD equation is the most advocated formula for calculating GFR is developed by the Modification of Diet in Renal Disease (MDRD) Study Group [26].

For Creatinine in mg/dl

$$eGFR = 186 \times \text{serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times [1.210 \text{ if black}] \times [0.742 \text{ if female}]$$

Many online calculators are available for calculating eGFR if serum creatinine values, age, sex and ethnicity of subject are known [27].

Non-surgical Periodontal Treatment (NSPT)

Subjects found to suffering from periodontitis were given non-surgical periodontal treatment. This is the conventional periodontal therapy involving scaling and root planing by removing or eliminating the etiologic agents like dental plaque, its products, and calculus- which are the root cause of inflammation, thus helping to establish a periodontium that is free of disease. This process is also called as deep-cleaning.

All subjects who received NSPT were recalled 6-8 weeks after the treatment. Serum CRP and kidney function tests were measured once again.

III. Results

After complete oral examination, those found to be suffering from periodontitis were given non-surgical periodontal treatment. Results are expressed as mean± standard deviation. ANOVA is used for comparison of baseline mean values of various parameters between different groups. Baseline values significantly different from controls have been highlighted. For comparison of pre-treatment and post-treatment values, dependent sample t-test has been used. P values less than 0.05 are considered significant. Chi-square test has been used to find association between CKD and presence of periodontitis and odds ratio has accordingly been calculated.

Table 3: Number of Subjects with Periodontitis

Sr no	Stage	Patients Enrolled	Patients with Periodontitis	Percentage
1.	Controls	50	22	44
2.	1+2	50	30	60
3.	3+4	50	40	80
4.	5	50	40	80

Percentage of patients with periodontitis is highest in patients in the later stages of CKD (dialysis and pre-dialysis stage), followed by CKD stage 1&2 while it is least in the controls. Two patients of stage 5 CKD died during the period between first and second sample collection and hence only 38 of the total 40 patients completed the study. Both patients who did not complete the study had severe periodontitis.

There is not much of statistically significant association between Periodontitis and CKD 1 &2 stage at P= 0.1093 but these patients have 1.9 times increased odds of having periodontitis as compared to controls. (95% CI= 0.86- 4.23)

There is a highly significant association between Periodontitis and CKD 3 &4 stage at P= 0.0002. The patients of CKD 3 &4 stage have 5 times increased odds of having periodontitis as compared to controls. (95% CI= 2.09- 12.4)

***Results from OpenEpi, Version 3, open source calculator—Two by Two [28]**

CKD stage 5 group also has 40 subjects with periodontitis. Hence, the odds ratio for periodontitis in this group is similar to that of CKD stage 3 & 4.

This means that patients with CKD stage 3, 4 and 5 are more than 5 times as likely to have periodontitis as compared to those without CKD.

Table 4: Periodontal Status of Controls and Patients with CKD

Sr no	STAGE	MILD	%	MODERATE	%	SEVERE	%
1.	Controls	09	22.7	08	36.4	05	40.9
2.	1+2	09	30	12	40	09	30
3.	3+4	05	12.5	15	37.5	20	50
4.	5	03	7.9	12	31.6	25	60.5

Table 5: Comparison of Periodontal Parameters in Different Groups

Sr No	PARAMETER	CONTROLS	CKD 1&2	CKD 3&4	CKD 5
1.	NO OF TEETH	29.32±2.57	30.10±1.71	26.73±3.67	27.29±2.57
2.	PI	2.22±0.42	2.67±0.29*	2.80±0.26*	2.78±0.32*
3.	GI	1.95±0.63	2.19±0.46	2.54±0.47*	2.69±0.40*
4.	BOP(% SITES)	69.33±10.91	70.71±12.14	73.19±12.34	76.91±11.94
5.	PPD	4.52±1.61	4.04±1.46	5.08±1.31	6.34±1.35*
6.	CAL	4.71±1.66	4.23±1.46	5.34±1.36	6.61±1.38*

***Significantly different than controls**

Patients in CKD stage 1&2 have most number of teeth in mouth while CKD stage3&4 have significantly lesser number of teeth than controls. Plaque and gingival index scores increase with increasing severity of CKD and even though BOP increases with disease progression, it is not significantly higher than controls. As disease progresses, mean PPD and CAL also is found to be more with CKD stage 5 patients showing significantly increased values as compared to controls.

Table 6: Baseline Values and Post-Treatment Changes in CRP & Markers of Kidney Function

Sr no	GROUP	MEAN CRP (mg/dl)		MEAN eGFR (ml/min/1.73m ²)		MEAN UREA (mg/dl)	
		BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1.	CONTROLS	1.33±1.03	0.52±0.41*	94.41±17.25	97.09±15.33*	30.79±4.85	27.18±5.73*
2.	CKD 1&2	2.21±1.04	1.69±1.05*	83.27±14.81^	87.97±13.36^*	33.43±8.27	33.44±7.82
3.	CKD 3&4	5.89±3.13^	4.87±2.70^*	29.30±11.90^	34.03±14.01^*	72.36±28.47^	71.98±28.69^
4.	CKD 5	6.48±3.48^	5.12±3.05^*	12.13±4.36^	14.34±5.65^*	101.50±36.58^	101.62±35.95^

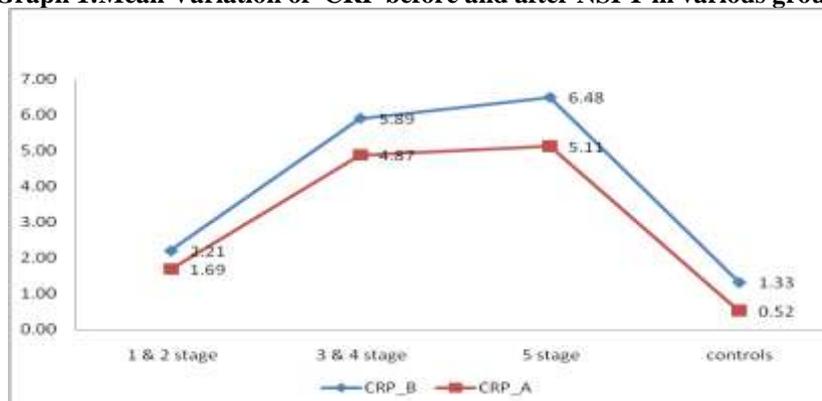
^significantly different from controls

*significant change after treatment

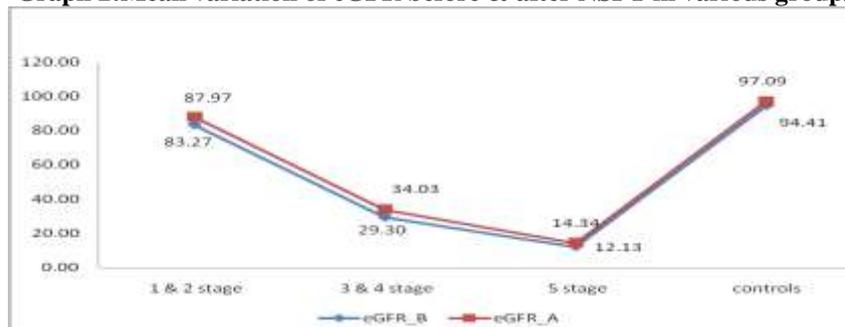
As expected, eGFR values decrease progressively as CKD progresses and it is significantly lesser than controls in all the groups. Serum urea and CRP values show increasing trend with CKD disease progression and are significantly higher than controls in later stages.

There is significant decrease in mean CRP values in controls as well as all groups of CKD patients after periodontal treatment. Significant improvement is seen in the eGFR values of all the groups even though all CKD groups have significantly lower eGFR values than controls. There is significant decrease in the serum urea values of controls after treatment. No significant change is observed in the serum urea values of any of the CKD group. The last two groups of CKD continue to have significantly higher urea levels than controls.

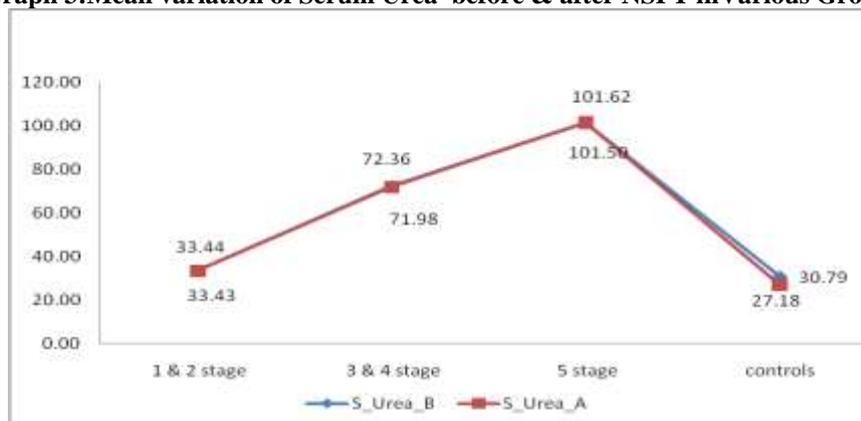
Graph 1: Mean Variation of CRP before and after NSPT in various groups



Graph 2: Mean variation of eGFR before & after NSPT in various groups



Graph 3: Mean variation of Serum Urea before & after NSPT in Various Groups



IV. Discussion

The present study found that periodontitis is prevalent in a large percentage of CKD patients as compared to controls (Table 3). 22 (44%) out of 50 controls were found to have periodontitis. In CKD stage 1&2, 30 patients (60%) had periodontitis, while in CKD stage 3&4 and CKD stage 5, 40 (80%) of the subjects had periodontitis. Table 4 shows the periodontal status of the subjects. Out of the 50 patients of stage 5 CKD, 40 (80%) had some or other form of periodontitis. 25 (62.5%) of these had severe periodontitis, 12 (30%) had moderate and 3(7.5%) had mild periodontitis. Two of the patients died before second sample could be collected. It is important to note that both of them had severe periodontitis. In Stage 3 & 4 CKD patients, 40 patients (80%) had periodontitis. Severe periodontitis was found in 20 (50%), moderate periodontitis in 15 (37.5%) and mild periodontitis was found in 5 (12.5%). In CKD stage 1 & 2, 30 patients (60%) had some or other form of periodontitis, of which 9 (30%) had severe, 12 (40%) had moderate and 9 (30%) had mild periodontitis. In the case of controls, 22 patients (44%) had periodontitis. Of these, 9 (40.9%) had severe, 8 (36.36%) had moderate and 5 (22.72%) had mild periodontitis. It is quite obvious that there is a higher prevalence of periodontitis in patients with CKD as compared to controls. The severity of periodontitis is also more in CKD group as compared to control group. The results of this study are in agreement with other studies in literature which also found higher prevalence of periodontitis and poor oral hygiene in patients with renal disease as compared to systemically healthy controls [29-32]. The severe periodontal inflammation in these patients could have contributed to the level of their renal disease burden. Many other studies have reported increased prevalence of periodontitis in the CKD population, but most of them have considered ESRD patients on HD.

CKD patients frequently have increased oral problems including xerostomia and altered salivary pH in addition to poor oral hygiene as reflected by increased plaque, calculus formation, and gingival inflammation. The uremic syndrome in HD patients is associated with immune dysfunction, including defects in both lymphocyte and monocyte function that could permit the overgrowth of periodontopathic bacteria. Lastly, patients with CKD who are on renal HD are under tremendous psychological stress and have severe time constraints due to which maintaining optimal oral hygiene and obtaining professional dental care may not be in their list of priorities [33].

Table 5 shows the comparison of baseline periodontal parameters in different groups. Significant difference does not exist within groups with regard to the mean number of teeth in patients. Only group 3 have significantly lesser number of teeth than controls. Patients in the CKD group exhibit higher PI, GI and BOP as compared to control group. The scores in these parameters are least in the control group and increase with severity of CKD with CKD stage 5 patients showing maximum values. BOP in CKD group does not vary significantly from controls. Patients in the CKD group also demonstrate significantly higher PPD and CAL than patients in the control group. All groups of patients responded well to the NSPT, showing significant improvement in all periodontal parameters, 6-8 weeks after treatment.

As expected, CKD group shows lower mean eGFR as compared to control group. Mean urea levels are lowest in the control group while the last two groups have significantly higher urea levels as compared to controls. CRP levels are markedly higher in CKD group owing to the inflammatory burden of the renal disease (Table 6).

NSPT had a positive effect on the eGFR of all subjects. Controls as well as patients in all stages of CKD showed significant improvement in eGFR as calculated by MDRD study equation (Table 6, Graph 2).The improvement in eGFR did not change the CKD stage of any subject, but it would be interesting to study the effect over a longer time-period. The results are in agreement with that of Artese et al [32] who also found that pre-dialysis CKD patients not just showed an improvement in periodontal parameters but also showed improvement in eGFR values as calculated by MDRD study equation while it differs from those of Graziani et

al [34] who found that GFR, as assessed by cystatin C levels, may be positively affected by NSPT but found no differences in GFR calculated by MDRD.

Serum urea levels of controls show a significant decline after NSPT while no change is observed in the CKD group (Table 6, Graph 3). No data is available in literature of effect of NSPT on serum urea levels. Whether NSPT played any role in decreasing the serum urea levels is not clear. The benefit of periodontal therapy is reflected in the significant decrease seen in the CRP levels in controls as well as CKD patients (Table 6, Graph 1). Studies available in literature report similar results in inflammatory markers in both CKD patients and healthy subjects with periodontitis[35-37] although not all of them report significant changes in the levels of all markers of inflammation[38].

Although there may be multiple causes for elevated CRP levels in ESRD patients, many of them experience high serum CRP values without visible signs of infection and/ or inflammation the causes of which are not entirely understood, but lately, it is becoming evident that this is one of the strongest predictors of poor clinical outcome in these patients [39], so it is extremely important to control inflammation. Since periodontitis is an inflammatory condition, its treatment and management will help to reduce the proinflammatory burden in CKD patients. CRP is a marker of inflammation and lowering of its levels is extremely beneficial for the patient as indicated by the study of Mattila et al [40] who measured CRP and fibrinogen levels before and after NSPT and found that decrease in CRP levels observed in their study was of the same magnitude as the differences in CRP levels that have been shown to be associated with increased CHD risk in several studies. They say that the association of CRP with various indicators of poor periodontal status may be more consistent than that of fibrinogen and it might therefore be more sensitive to the treatment effect. Many other studies have reported beneficial systemic effects of NSPT like improved endothelial function, decrease in systolic and diastolic blood pressure, an increase in plasma levels of HSP10 (anti-inflammatory factor), decrease in total WBC count, increased haemoglobin, reduction in the load of oral pathogens resulting in reduction in serum inflammatory markers and a reduction in arterial intima- media thickness (IMT) [41-48]. The results of Piconi et al[48] indicate that after periodontal treatment, there is a reduction in CD44, which is an adhesion protein expressed on inflammatory and vascular cells that allows the adhesion of activated lymphocytes to endothelium and smooth muscle thus promoting recruitment of macrophages into the atherosclerotic lesion. They conclude that periodontal treatment would result in diminished seeding of the vessel walls by oral pathogens which in turn would diminish local inflammation, reduce infiltration of the vessels by circulating leukocytes and ultimately partially reverse thickening of the vessel walls.

However, Ide et al [49] and Yamazaki et al [50] did not find any decrease in serum levels of inflammatory cytokines after non surgical periodontal treatment though the second study did find insignificant reductions in hs-CRP values indicating that the treatment does decrease systemic inflammatory burden. D'Aiuto et al [51] also caution in their review article that although NSPT may reduce CRP levels and improve endothelial function, there is limited evidence of its beneficial effects on reducing inflammatory cytokines, Leukocytes, lipid levels and blood pressure.

Piconi et al [48] are of the opinion that the beneficial effect of NSPT is time-limited as the clinical, immunological and biochemical markers tended to increase in 12 months of treatment, even with a sufficiently reduced bacterial load indicating that perhaps even low bacterial loads are enough to trigger immune activation. In the words of Cobb, "Even when chronic periodontitis is treated successfully, the reduction in subgingival pathogenic microbes is transitory. Thus, the need for follow-up treatment, usually consisting of supra-and subgingival debridement at 3 to 4 month intervals, is necessary to maintain the initially gained beneficial effects". [52]End-stage renal disease substantially increases the risks of death, cardiovascular disease, and use of specialized health care, but the effects of less severe kidney dysfunction on these outcomes are less well defined. Go AS et al [53] studied these outcomes in a large population and found that the risk of death and hospitalization increased as the GFR decreased below 60 ml/min/1.73m² highlighting the clinical and public health importance of chronic renal insufficiency. A systematic review published in 2013 reported that all interventional studies have found positive effect of periodontal treatment on eGFR[54]. In view of these facts, a lot of emphasis needs to be laid on maintaining good oral hygiene. Patients with CKD should undergo regular periodontal examination and treatment.

V. Conclusions

The present study has found a very high prevalence of chronic periodontitis in subjects with chronic kidney disease. The periodontal therapy involving scaling and root planing has been found to decrease serum C-RP and improve eGFR in these subjects. Chronic inflammation is a risk factor for atherosclerosis and cardiovascular morbidity and mortality frequently seen in these patients. Nearly half of the CKD patients may have Type 2 diabetes, which has been historically associated with the incidence and severity of periodontitis. Despite all the controversial results and speculations, present results indicate that NSPT has beneficial effects on CKD patients. Regardless of the poorly understood relationships between renal disease, chronic inflammation,

and periodontal infections, it is reasonable to increase our efforts to prevent, diagnose, and treat periodontal disease in these patients. CKD patients may be less prone to pay attention to oral hygiene due to immense psychological, financial and emotional burden of the disease. Emphasis on oral care or addressing oral healthcare issues is not on the priority list of either the patient or the attending physician. Periodontitis is a disease that cannot be ignored and its treatment should be given utmost importance. The risks associated with the treatment of periodontitis are low and are outweighed by therapy-mediated benefits. Non-surgical periodontal therapy need not be in adjunct with any medication that may result in adverse side effects. Patient education, motivation, enhanced oral hygiene maintenance and regular periodontal care are extremely important during renal treatment. Improving periodontal health may reduce the inflammatory burden in renal diseases and improve overall health. Large scale epidemiological studies are needed to give further credence to these results. The CKD registry can play a larger role by initiating studies to look at prevalence of periodontitis in the patients with CKD and increasing oral hygiene awareness among the general population. Close cooperation between the periodontist and nephrologist can ensure excellent results in this era of inter-disciplinary approach.

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