Comparative evaluation of the left ventricular mass in patients with chronic kidney disease in periodontally healthy, chronic gingivitis, and chronic periodontitis patients

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ABSTRACT

Objectives: Emerging evidence suggests that inflammation due to periodontal diseases may not be limited to adjacent oral tissues but may have influence on systemic diseases such as chronic kidney diseases (CKD) and cardiovascular diseases. Hence, this study was aimed to evaluate and compare left ventricular mass (LVM) in patients with CKD undergoing hemodialysis (CKDH) in periodontally healthy, chronic gingivitis, and chronic periodontitis.

Methodology: A total of 60 patients diagnosed with CKDH were divided equally into three groups based on periodontal status as CKDH patients with healthy periodontium (Group I), CKDH patients with chronic gingivitis (Group II), and CKDH patients with chronic periodontitis (Group III). These patients were assessed clinically, biochemically, and echocardiographically. LVM in each of these patients was calculated according to Devereux formula and was indexed to height.

Results: Group II and Group III patients exhibited higher mean LVM of 199.51 ± 40.17 g and 200.35 ± 65.04 g, respectively, as compared to Group I of 161.56 ± 27.99 g. Similarly, LVM index (LVMI) was found to be more in Group II and Group III at 59.36 ± 13.14 g/m$^{2.7}$ and 57.83 ± 19.94 g/m$^{2.7}$, respectively, while it was 45.99 ± 11.87 g/m$^{2.7}$ for Group I patients.

Conclusion: Increasing the severity of periodontal diseases in CKDH patients is associated with increase in LVM and LVMI. Periodontal screening and intervention would enable the clinician to refine cardiovascular risk assessment in such patients.

Keywords: Chronic gingivitis, chronic kidney disease undergoing hemodialysis, chronic periodontitis, healthy periodontium, left ventricular mass

Introduction

Periodontal diseases are chronic polymicrobial conditions caused by Gram-negative microorganisms in a susceptible host.[1] The disease are clinically characterized by gingival inflammation, which if not controlled, may lead to destruction of alveolar bone with consequent tooth loss. It is suggested that periodontal diseases do not frequently occur as a consequence of plaque deposition, but are also accompanied with distinct host factors which alter the impact of plaque in a particular individual. The current literature indicates a positive association of periodontal diseases with a wide array of systemic diseases and conditions.[2,3] The microbial pathogens causing periodontal disease incite local and systemic inflammatory response that is hypothesized to cause endothelial damage and promote atherosclerosis.[4,5]

Chronic kidney disease (CKD) patients often placed on hemodialysis are known to have an increased risk of atherosclerotic complications which occur much earlier and are more advanced than in the general population.[6] It is evident that inflammation assumes a central role in the pathogenesis of these complications which are routinely monitored through levels of systemic markers such as C-reactive protein (CRP). Although multiple mechanisms exist which may lead to elevation of CRP values in patients with CKD undergoing hemodialysis (CKDH), there are many patients who demonstrate these elevated values even in the absence of overt infection or inflammation.

Periodontal diseases are of common occurrence in the general population and are diagnosed based on the severity of inflammation and infection. These have also been associated

with an increased prevalence of atherosclerotic complications as well as elevated levels of CRP.

Since periodontal screening is not routinely undertaken as a part of the assessment of CKDH patients, there is a great possibility of periodontal diseases being overlooked as a source of inflammation in CKDH patients. It is hypothesized that the differing severity of periodontal diseases due to the inflammatory component would have an incremental effect over the atherosclerotic changes occurring in such patients.

One of the eminent prognostic signs in cardiovascular events is the left ventricular hypertrophy (LVH) which is caused by an increase in the mass of the left ventricle and is secondary to an increase in wall thickness and/or an increase in cavity size. Preliminary investigations reveal that periodontal diseases may have a direct or indirect association with an increased left ventricular mass (LVM).[7,8]

There appears to be a paucity of understanding with regard to the association of differing severity of periodontal disease in CKDH patients and an increase in LVM and hence it was thought imperative to further clarify this relationship. Hence, this study was planned to evaluate and compare LVM in CKDH patients with periodontally healthy, chronic gingivitis, and chronic periodontitis.

Methods

The study population comprised 60 patients diagnosed with CKD and visiting the Department of Medicine for hemodialysis therapy. The study protocol was explained to the patients, and written informed consent was obtained from them. The study was initiated following approval from the Institutional Ethics Committee and adhered to the provisions of Helsinki Declaration. It was registered with the Clinical Trial Registry of India, which is Primary Register of the International Clinical Trials Registry Platform. The patients were screened for periodontal parameters at the department of periodontics of our institute. A specially designed pro forma was used to record information and observations which included a detailed case history, clinical examinations, periodontal screening, biochemical, and echocardiographic parameters.

The sample size (n) for this study was estimated using the formula

$$n = \{\sigma^2 \, (Z_\beta - Z_\alpha)^2\}/\Delta^2$$

Where, Z_α (significance level at 5%) is set at 1.96;
$Z_\beta = 80\% = 0.8416$ is also constant set by convention according to power of study
σ = s.d. (standard deviation) = 31.61
Δ = Confidence interval = 5

Taking the significance level at 5% the sample size was calculated with 80% power for comparing the LVM in CKDH patients with periodontal disease. The sample size was estimated to be 56.3, which was rounded-off to 60 (20 subjects per group).

The study has been conducted in the period from January 2017 to June 2017. During this study period, a total of 72 patients were recognized as CKDH patients as per our study criteria. The patients with any other systemic diseases were excluded from our study. Of these, 12 patients did not have regular follow-up and incomplete data regarding study protocol. Hence, these 12 patients were excluded and final sample size was taken, as a total of 60 numbers of patients.

All the patients in the study population were above 40 years of age (mean age 50.23 ± 8.82 years) and were segregated into three groups as Group I: CKD patients on hemodialysis with healthy periodontium as assessed by gingival index < 1 and probing pocket depth < 3 mm with no attachment loss (AL); Group II: CKD patients on hemodialysis with chronic gingivitis assessed by gingival index ≥ 1, probing pocket depth < 3 mm, and no AL; and Group III: CKD patients on hemodialysis with severe chronic periodontitis as assessed by gingival index ≥ 1, probing pocket depth ≥ 5 mm, and AL ≥ 5 mm.

Inclusion criteria

1. All the patients diagnosed with CKD and receiving hemodialysis therapy
2. Chronic periodontitis was diagnosed according to the International Workshop for classification of periodontal diseases organized by AAP, 1999 characterized by at least 8 sites with probing pocket depth of ≥ 5 mm and AL of ≥ 5 mm.

Exclusion criteria

The following criteria were excluded from the study:
1. History of any periodontal treatment in the past 6 months
2. Self-reported smokers and alcoholics
3. Pregnant or lactating mothers
4. Patients with gestational diabetes
5. Patients with symptoms of acute illness or extraoral infection.

Chronic periodontitis was diagnosed according to the International Workshop for classification of periodontal diseases organized by AAP, 1999 characterized by at least 8 sites with probing pocket depth of ≥ 5 mm and AL of ≥ 5 mm.[9] Patients with history of any periodontal treatment in the past 6 months, self-reported smokers and alcoholics, pregnant or lactating mothers or patients with gestational diabetes and those with symptoms of acute illness or extraoral infection were excluded from the study.

Clinical parameters

Periodontal probing depth and AL were measured using Williams graduated periodontal probe[‡] on four sites on each tooth. Assessment of periodontal status also included recording of plaque index[10] and gingival index.[11] Parameters used to calculate body mass index (BMI) such as height in meters, weight in kilograms were recorded along with the waist circumference. BMI calculation was done with the formula:

$$BMI = \frac{Weight\,(kg)}{Height\,(m^2)}$$

The study participants were categorized based on the World Health Organization criteria.[12]

Diastolic and systolic in-office blood pressure was recorded as a mean value expression of three consecutive readings separated by 5 min intervals using the auscultatory technique with a mercury sphygmomanometer. The data on demographic parameters for all the patients in each of the study groups were also recorded.

Biochemical parameters

Area over the antecubital fossa was disinfected to withdraw blood. 2 ml of blood was obtained and the samples were stored until analysis at −80°C for evaluation of biochemical parameters. These included glycated hemoglobin (HbA1c)[§], serum creatinine[k], and CRP[¶]. All laboratory values were obtained by automated and standardized methods in laboratory of the department of biochemistry of our institute.

Electrocardiographic parameters

Dimensions of the left ventricle were assessed with two-dimensional echocardiography[#]. The procedure involved use of a 3 MHz cardiac probe which was operated by a trained sonographist. To exclude atherosclerotic plaques and endocardial vegetation, B − mode presentation was applied and M − mode presentation was used. These readings were obtained for every patient and the average value was calculated as the respective LVM according to Devereux formula.[13]

The results were drawn based on the formula

$$LVM_{corrected} = 0.8 \times LVM + 0.6 \text{ (expressed in g) and}$$

LVM index (LVMI) was obtained by dividing the $LVM_{corrected}$ by height[2.7] and expressed as $g/m^{2.7}$.

All the clinical, biochemical, and electrocardiographic parameters were obtained by three different examiners (RK), (KS), and (AM), respectively, who were not aware about the other parametric measurements.

At the start of the data gathering, the measurements on 10% of the sample were repeated by the examiner to obtain the intra-examiner evaluation. The reproducibility and concordance of clinical measurements were estimated by means of Cronbach's coefficient, which was found to be 0.85 for the study population, thereby proving the efficacy of the calibration.

Statistical analysis

Statistical analysis was performed using SPSS v16. Frequency distribution and descriptive statistics such as mean and standard deviation were obtained for demographic parameters. Furthermore, descriptive statistics were obtained for periodontal parameters and compared across three groups. Anthropometric parameters such as BMI, waist circumference, and biochemical parameters such as serum creatinine, CRP, and glycemic control parameter (HbA1c) were also compared across groups using one-way analysis of variance (ANOVA). LVM and LVMI were compared across study groups using one-way ANOVA. Variables which showed significant difference across the three group bivariate analysis were included in multivariate analysis. Multivariate analysis was applied using multiple logistic regression (enter method). In the analysis, $P < 0.05$ was considered significant.

Results

The present study evaluated the LVM in patients diagnosed with CKDH in periodontally healthy and differing severities of periodontal disease. The mean age of the patients in all the three groups was 50.23 ± 8.82 years (41 males and 19 females). Anthropometric parameters such as BMI and waist circumference when compared across the groups showed a steady decline of mean values from Group I to Group III, as depicted in Table 1.

The periodontal parameters of pulsatility index and gastrointestinal indicate a considerable and consistent increase from Group I $(0.96 \pm 0.33 \text{ and } 0)$ to Group II $(1.75 \pm 0.30 \text{ and } 1.46 \pm 0.39)$ to Group III $(2.38 \pm 0.31 \text{ and } 2.27 \pm 0.27)$. These differences were found to be statistically significant, as shown in Table 1.

The biochemical parameters of HbA1c, serum creatinine, and CRP were compared across the groups using one-way ANOVA and also followed the trend of consistent increase in values from Group I to Group III. The mean values of HbA1c in Group I were $4.95 \pm 1.50\%$ while these values in Group III were $6.36 \pm 1.90\%$. Similarly, the serum creatinine values increased from 7.46 ± 2.50 mg/dL in Group I to 8.04 ± 1.56 mg/dL in Group II to 8.31 ± 2.72 mg/dL in Group III, respectively. However, these values were not found

to have statistical significance. The mean CRP values were maximum in Group III (4.30 ± 3.52 mg/L) and minimum in Group I (0.61 ± 0.69 mg/L) and yielded statistical significance, as depicted in Table 1.

The echocardiographic parameters of mean LVM and LVMI were compared across the groups using one-way ANOVA. The mean LVM for Group I was 161.56 ± 27.99 g which increased to 199.51 ± 40.17 g in Group II and was the maximum of 200.35 ± 65.04 g in Group III. These findings were statistically significant. The LVMI values also revealed an increase from 45.99 ± 11.87 g/m$^{2.7}$ in Group I to 57.83 ± 19.94 g/m$^{2.7}$ in Group III, as depicted in Table 1.

It was revealed that the number of patients with hypertension was least in Group I with 8 patients and the most were found in Group III with 10 patients, though the difference was not significant. There was a consistent rise in the systolic and diastolic blood pressure from Group I to Group III, as depicted in Table 2.

When the multivariate logistic regression analysis was performed, it was revealed that Group II and Group III are

1.3 times and 2.7 times likely to have higher LVM scores, respectively, as compared to Group I, as depicted in Table 3.

Discussion

The link between CKD and CVD was first recognized by Bright in 1836, who found evidence of marked LVH on autopsy in patients who had albuminuria.[14] Moreover, the Joint British Societies for the prevention of cardiovascular disease has recognized CKD as a risk factor for cardiovascular disease, independent of other factors.[15] A large number of traditional risk factors for cardiovascular disease are common to the CKD population.

Some of the previous reports in the literature suggest that the prevalence of chronic periodontitis in CKDH patients is nearly 40%.[6,16] It is evident that inflammation within the tissues plays a central role in patients on hemodialysis and in patients with periodontal diseases.[17,18] It has also been reported that periodontal disease with type 2 diabetes mellitus is associated with an increased LVM.[8,19] However, there seems to be paucity of literature with regard to influence of

Table 1: Comparison of clinical, biochemical, and echocardiographic parameters between chronic kidney disease undergoing hemodialysis patients with healthy periodontium (Group I), chronic gingivitis (Group II), and chronic periodontitis (Group III)

Characteristics	Group I (*n*=20)	Group II (*n*=20)	Group III (*n*=20)	*P*-value*
Age (years)	50.25±8.12	48.3±6.9	52.15±11.02	0.39
Waist circumference (cm)	95.35±12.66	99.45±10.26	94.75±10.49	0.35
BMI (kg/m²)	21.03±2.78	20.35±2.64	19.73±2.60	0.31
Periodontal probing depth (mm)	1.49±0.32	1.59±0.32	5.83±0.96†	<0.001
CAL (mm)	0	0	6.24±1.05†	<0.001
Plaque index	0.96±0.33†	1.75±0.30†	2.38±0.31†	<0.001
Gingival index	0†	1.46±0.39†	2.27±0.27†	<0.001
Systolic BP (mmHg)	136.6±12.91	138.5±8.82	145.3±14.99	0.07
Diastolic BP (mmHg)	80±18.42	85.1±5.89	91.5±9.5†	0.01
Glycated hemoglobin (%)	4.95±1.50†	5.98±1.81	6.36±1.90†	0.03
Serum creatinine (mg/dl)	7.46±2.50	8.045±1.56	8.31±2.72	0.49
CRP	0.61±0.69	1.67±0.77	4.3±3.52†	<0.001
LVM (g)	161.56±27.99	199.51±40.17	200.35±65.04†	0.01
LVMI (g/h$^{2.7}$)	45.99±11.87	59.36±13.14	57.83±19.94	0.01

Group I: Chronic kidney disease patients with healthy periodontium, Group II: Chronic kidney disease patients with chronic gingivitis, Group III: Chronic kidney disease patients with chronic periodontitis. All values presented as mean±SD (range). *Calculated using One-way analysis of variance with *P*<0.05. †Indicates statistically significant difference at *P*<0.05 by *post hoc* Turkey test. LVM: Left ventricular mass

Table 2: Association of hypertension with chronic kidney disease undergoing hemodialysis patients with healthy periodontium (Group I), chronic gingivitis (Group II), and chronic periodontitis (Group III)

Cardiovascular Status	Group I (*n*=20) (100%)	Group II (*n*=20) (100%)	Group III (n=20) (100%)	*P*-value‡
HTN				
Non-hypertensive	12	11	9	0.72
	60.00	55.00	47.40	
Hypertensive	8	9	10	
	40.00	45.00	56.60	

Group I: Chronic Kidney Disease patients with healthy periodontium, Group II: Chronic Kidney Disease patients with chronic gingivitis, Group III: Chronic Kidney Disease patients with chronic periodontitis. All values presented as mean±SD (range). ‡Calculated by Chi-square test

Table 3: Significant correlations of CAL, CRP, LVM, and LVMI after multivariate logistic regression analysis showing adjusted OR with 95% CI

Parameters	Odds Ratio (CI)	*P*-value
CAL		
Group I	-	-
Group II	0.86 (0.38–1.54)	0.6
Group III	1.89 (1.41–2.70)	0.02
CRP		
Group I	-	-
Group II	0.92 (0.30–2.51)	0.69
Group III	2.16 (1.21–3.90)	0.04
LVM		
Group I	-	-
Group II	1.3 (0.79–1.71)	0.09
Group III	2.71 (2.08–3.1)	<0.01
LVMI		
Group I	-	-
Group II	1.55 (0.87–2.16)	0.07
Group III	3.3 (2.16–4.05)	0.01

Group I: Chronic kidney disease patients with healthy periodontium, Group II: Chronic kidney disease patients with chronic gingivitis, Group III: Chronic kidney disease patients with chronic periodontitis. CI: Confidence interval, OR: Odds ratio. LVM: Left ventricular mass

increasing severity of periodontal disease in CKDH patients and LVM.

In the present study, we have segregated the patients in different groups in such a way that they would reflect the differential inflammatory burden as observed in chronic gingivitis and severe chronic periodontitis and the patients were diagnosed according to the International Workshop for classification of periodontal diseases organized by AAP 1999. Some of the previous studies have diagnosed periodontal diseases based on CPITN scores[20,21] or phenotypic based classification of periodontal disease.[22] It is more appropriate to have used the currently acceptable classification which is the one we have used in the present study. Furthermore, the diagnosis of periodontal disease based on CPITN scores is widely used for epidemiological screening purposes while the phenotypic based classification does not take into consideration the attachment levels which are in fact more representative of the severity of periodontal diseases.

The serum HbA1c levels observed in the present study indicate that all the patients in all the groups were non diabetics and so the confounding effect of hyperglycemic status on the periodontal disease and also the cardiovascular risk was absent. According to Bergstroem *et al*., a close interdependent link between chronic low-grade inflammation and malnutrition and atherosclerosis exists which is consistent with the elevation of specific parameters such as acute phase reactants, the most predictable being CRP.[23] The CRP levels were found to be

increased in Group II and Group III when compared to Group I, which indicates that the local inflammatory component within the tissues led to the increase. This finding is consistent with those reported previously.[6,24] Furthermore, since patients with symptoms of acute illness or extraoral infections were excluded from the study, the increased levels can be attributed to the periodontal disease conditions in these patients.

The mean LVM in the present study increased from Group I and was found to be the maximum in Group III patients suggestive of the increase being related to the severity of the periodontal disease. The increase in LVM also correlated with the simultaneous increase in blood pressure which was observed in Group II and Group III. These findings are similar to those reported by Franek *et al*.[21] However, the patients included in the concerned study had diabetic patients with higher HbA1c levels. Hence, the influence of diabetes mellitus over severity of periodontal diseases and LVM cannot be ruled out. In contrast, in the present study, since the patients were nondiabetic, this confounding influence was absent.

Patients with CKDH demonstrate "inflammatory malnutrition," which is meticulously connected to the presence of an inflammatory state, markedly elevated oxidative stress, increased protein catabolism, cardiac and vascular comorbidities, and an inability to reverse the malnutrition.[25] It has been reported that periodontal diseases could indeed be considered as emerging risk factor in cardiovascular events.[26] Since periodontal pathogens were found in atherosclerotic plaques, it is possible these microorganisms may play a direct role in plaque formation.[27] The systemic inflammation precipitated by periodontal disease may also be associated with atherosclerosis which leads to cardiovascular events. In addition, atherosclerosis induces arterial stiffness and resulting into hypertension. Hence, from the results of the present study, it can be assumed that the increasing severity of periodontal disease could be one of the primary reasons for increase in LVM. Periodontal infection is also associated with elevated serum concentration of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α.[28] Inflammatory cytokines, including TNF-α and IL-1β, may play an important role in the pathogenesis of myocardial failure. These and other inflammatory cytokines can regulate growth and gene expression in cardiac myocytes and other cells present in the myocardium.[29]

The mean LVM in Group III in present study was 200.35 ± 65.04 g, while it was bit higher at 238.6 g in chronic periodontitis in the study of Franek *el al*.[19] The difference in these observations can be attributed to the differences in ethnicity and methods of evaluation of periodontal status by the concerned authors. The LVMI when compared across the groups followed the trend of increase from Group I to Group III.

The present study being cross-sectional in design does not permit us to assess the cause – effect relationship between

the various parameters examined. Further prospective and periodontal interventional studies are desired to elaborate on a detailed influence of these parameters.

Conclusion

It can be stated that increasing severity of periodontal diseases in CKDH patients is associated with increased LVM and also with higher blood pressure in these patients. Regardless of the exact underlying mechanisms, it may however be said that an increase in LVM is an independent cardiovascular risk factor leading to cardiovascular morbidity and mortality. Mandatory periodontal screening of the patients affected with CKD will enable the scientific and clinical communities to refine the cardiovascular risk assessment.

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