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Significance of elevated gingival crevicular fluid tumor necrosis factor-α and interleukin-8 levels in chronic hemodialysis patients with periodontal disease

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Background and Objective: The prevalence of chronic renal disease in industrialized countries is increasing, and chronic renal disease and periodontitis can have significant, reciprocal effects. The aim of this study was to evaluate the associations between specific clinical parameters and the levels of tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) in the gingival crevicular fluid of hemodialysis (HD) patients with periodontal disease.

Material and Methods: Forty-three HD patients and 43 systemically healthy subjects were enrolled in this study. Plaque index (PI), gingival index (GI) and pocket depth were used to determine periodontal status. Venous blood samples were obtained from each patient in the morning before the dialysis session and analyzed to determine the levels of inflammatory, biochemical and hematological parameters. Gingival crevicular fluid was collected from all subjects, and the levels of TNF-α and IL-8 were determined in the gingival crevicular fluid samples.

Results: The following results were obtained from HD patients and controls: TNF-α (pg/mL), 31.40 ± 1.46 and 3.06 ± 0.15 ($p < 0.001$); IL-8 (pg/mL), 90.98 ± 94.03 and 35.05 ± 16.86 ($p < 0.001$); PI, 1.69 ± 1.02 and 0.04 ± 0.02 ($p < 0.001$); GI, 0.82 ± 0.06 and 0.04 ± 0.02 ($p < 0.001$); and pocket depth, 2.23 ± 0.63 and 1.51 ± 0.05 ($p < 0.001$), respectively. In addition, there were positive correlations between TNF-α and PI ($r = 0.642$, $p < 0.001$), between TNF-α and GI ($r = 0.565$, $p < 0.001$), between TNF-α and pocket depth ($r = 0.522$, $p < 0.001$), between IL-8 and PI ($r = 0.402$, $p = 0.002$), between IL-8 and GI ($r = 0.396$, $p = 0.002$), and between IL-8 and pocket depth ($r = 0.326$, $p = 0.012$). There were negative correlations between albumin and PI ($r = -0.491$, $p < 0.001$), albumin and GI ($r = -0.406$, $p < 0.001$), albumin and pocket depth ($r = -0.464$, $p < 0.001$) and albumin and CRP ($r = -0.467$, $p = 0.002$) and between the gingival crevicular fluid levels of TNF-α and IL-8, TNF-α and hemoglobin ($r = -0.745$, $p < 0.001$; $r = -0.285$, $p < 0.05$) (respectively).

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Conclusion: The levels of TNF-α and IL-8 in gingival crevicular fluid were significantly higher in HD patients than in controls. There were strong, positive correlations between clinical periodontal parameters and the levels of inflammatory cytokines in gingival crevicular fluid from the HD patients.

Key words: hemodialysis; periodontal status; gingival crevicular fluid; tumor necrosis factor-α; interleukin-8

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Chronic renal failure (CRF) is caused by a progressive and irreversible decline in the number of functioning nephrons, and patients develop end-stage renal disease once the damage passes the point of compensation. Therefore, dialysis treatment and kidney transplantation are life-saving medical procedures in these patients (1–3).

The prevalence of chronic renal disease in industrialized countries is increasing, and when coupled with improved rates of survival for renal replacement therapies it is evident that patients with chronic renal disease will comprise an increasing proportion of dental patients in the near future. In addition, chronic renal disease and periodontitis can have significant, reciprocal effects (4).

Patients undergoing dialysis are more susceptible to infection because of general debilitation and depression of the immunological response. Furthermore, in patients using immunosuppressants following renal transplantation, persisting oral infections can have a severe clinical course and can even cause rejection of the transplanted kidney (5). Thus, it is important to recognize and treat periodontal diseases, in addition to other oral and dental conditions, in such patients.

Hemodialysis (HD) patients face a 25% annual mortality rate, with 50% of reported deaths attributed to cardiovascular disease. All-cause and cardiovascular mortality correlate with acute-phase proteins such as C-reactive protein (CRP). Hepatic CRP synthesis is upregulated by inflammation; however, elevated CRP values are frequently found in the absence of apparent infection or inflammation. Destructive periodontal diseases have been associated with elevated CRP levels (6); and destructive periodontal diseases in the general population have been associated with both an increased prevalence of atherosclerotic complications and an elevation in serum CRP values (7).

By contrast, although bacteria are the primary etiological factors in periodontal disease, the patient's immune response is a determinant of disease susceptibility, and dialysis also interferes with the immune response of the host. Thus, most recent studies focusing on the periodontal health of end-stage renal disease patients on HD maintenance therapy have indicated the presence of poor oral hygiene and attendant gingival inflammation (8–10). Most of the findings of these studies were associated with the clinical signs of the disease process, and limited data are available regarding the physiopathological effects of renal failure on oral and/or periodontal tissues. It is therefore necessary to investigate the possible relationships between these effects and clinical inflammatory parameters. Periodontal pathogens induce not only local inflammation and tissue destruction, but are also involved in systemic increases in inflammatory and immune responses (11).

This study was performed to evaluate the correlations between clinical parameters and the levels of both tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) in the gingival crevicular fluid (GCF) of HD patients with periodontal disease.

Material and methods

Selection of patients

The study population consisted of 43 HD patients (18–72 years of age; mean age 42.02 ± 17.05 years) and a control group of 43 healthy subjects (19–78 years of age; mean age 41.11 ± 16.13 years). The sample size of patients required in this study was estimated by power analysis (effected size, 0.9; delta, 2.98; alpha, 0.05; actual power, 0.90; critical (t), 1.68; total sample size, 44 patients). In the HD group, all patients received HD therapy three times a week, with each session lasting for approximately 4 h, in the dialysis centers of the Medical Faculty Hospital at the University of Dicle, Diyarbakir, Turkey. The study was designed as a cross-sectional clinical trial. None of the patients had received a periodontal examination or periodontal therapy for at least 6 month before the study. The subjects in the control group (n = 43) had no systemic disease, received treatment in a regular dental clinic and matched the CRF population in age and gender. All examinations were carried out by one of the authors. However, before recording the clinical data, the examiner (who is a specialist in Periodontology), calibrated the clinical examination. The examiner could not be blinded to the subject's general systemic condition because subjects were examined either in a hospital or in a regular clinic. However, the examiner was 'blind' to the subgroup of patients with renal failure.

The exclusion criteria were the existence of cardiovascular disease (congestive coronary deficiency coronary artery disease, unstable angina pectoris, postmyocardial infarction, dysrhyhmia), diabetes mellitus and signs of systemic or local infection/inflammation (e.g. vascular access infection, malignancy, upper respiratory tract infection) except periodontal disease. It was mandatory for the patients to have periodontal disease as gingivitis or periodontitis.

The protocol was explained to the subjects, all of whom gave their written informed consent to participate in the study. Demographic characteristics of the participants, such as gender, age, duration of HD and urea reduction rate, were obtained from the registry of the HD center. Blood samples were taken in the morning of

the HD session and the levels of hemoglobin (Hb), leukocytes, albumin, C-reactive protein (CRP), serum creatinine and serum urea in the samples were determined by staff in the central laboratory of the Medical Faculty Hospital.

The control group, which consisted of 43 patients from the companion of the patients in the dental clinic was matched for both age and gender to the HD group (Table 1). The main selection criteria for the control group were (i) absence of systemic problems and (ii) periodontal health. The main limitation of the study was the small number of control subjects.

Clinical recordings

Before clinical examination, a detailed medical history was recorded for all participants. Periodontal indices were recorded between 10:00 and 11:00 h (before a midweek HD session) in the HD group and during the same time-period in the control group using a dental mirror, explorer and a periodontal probe with Williams markings.

Before crevicular fluid collection, supragingival plaque was scored using the plaque index (PI) (12). Gingival inflammation was scored after the collection of crevicular fluid using the gingival index (GI) (13). Pocket depth (the distance from the free gingiva to the bottom of the gingival sulcus using a Williams probe) was used to identify periodontal disease in patients on the day before the HD session. Then, we grouped the patients as having periodontitis or gingivitis, according to their pocket depth.

Periodontal probing was performed at six sites for every tooth, excluding the third molars, using a periodontal probe with Williams markings. The probe was directed parallel to the long axis of the tooth. None of the patients had a history of periodontal therapy within the previous 6 month, and none had they taken antibiotics within the previous 3 month. All clinical data were recorded by one examiner.

Crevicular fluid sampling

After removal of supragingival plaque from each tooth, the individual tooth site was gently air-dried and isolated using cotton rolls. A saliva ejector was used to avoid salivary contamination of the samples. Samples of gingival crevicular fluid were collected using paper strips (Periopaper; ProFlow, Amityville, NY, USA) from the mesiobuccal aspects of teeth 4 or 5 in the upper left jaw of all patients. The paper strips were inserted consecutively into the crevice at the mesial or distal midpoints until mild resistance was felt. The strips were left *in situ* for 30 s and then transferred into microcentrifuge tubes and stored at −20°C until the day of analysis. Before analysis, the samples were placed in centrifuge tubes to which 1 mL of 9% sodium chloride (9 mg/mL) solution was added. After storage at +4°C for a further 18 h (14), the levels of TNF-α and IL-8 in the samples were determined, in an IMMULITE 1000 Automated Immunoassay System (Diagnostic Products Corporation, Los Angeles, CA, USA) device, by analysis of chemiluminescent immunometric assay (15). The analytic sensitivity of this device for TNF-α is 1.7 pg/mL and for IL-8 is 2 pg/mL. Serum samples were also collected from patients immediately before the dialysis session using gingival crevicular fluid sampling.

Statistical analysis

Statistical analyses were performed using the Student's *t*-test for continuous variables, the chi-square test for categorical variables and Pearson's correlation. The data are shown as means ± standard deviation, and a *p*-value of < 0.05 was considered significant.

Results

Clinical characteristics

Forty-three HD patients (20 men and 23 women; mean age 42.02 ± 17.05 years) and 43 healthy controls (21 men and 22 women; mean age 41.11 ± 16.13 years) were enrolled in the study.

There were no significant differences between the groups in terms of demographic characteristics (e.g. age or gender). However, there were significant differences in periodontal parameters ($p < 0.001$; Table 1) and in various hematological parameters (e.g. serum creatinine, serum urea, Hb, CRP and albumin levels; $p < 0.001$; Table 2) between the HD and control groups.

Among 15 patients with periodontitis, four patients had mild periodontitis, six had moderate periodontitis and five had severe periodontitis. Among patients with gingivitis, 19 had mild gingivitis, eight had moderate gingivitis and one had severe gingivitis. The periodontal characteristics of the patients are presented in Table 3.

Gingival crevicular fluid levels of IL-8 and TNF-α

The levels of TNF-α and IL-8 in the gingival crevicular fluid were

Table 1. Clinical characteristics of the study population

Parameter	Patients ($n = 43$)	Control group ($n = 43$)	*p*-Value
Age	42.02 ± 17.05	41.11 ± 16.13	0.732
Gender (m/f)	20/23	21/22	0.850
HD time (mo)	36.0 ± 1.70	–	–
PI	1.69 ± 1.02	0.04 ± 0.02	< 0.001
GI	0.82 ± 0.06	0.04 ± 0.02	< 0.001
PD	2.23 ± 0.63	1.51 ± 0.05	< 0.001
GCF TNF-α (pg/mL)	31.40 ± 1.41	3.06 ± 0.15	< 0.001
GCF IL-8 (pg/mL)	90.98 ± 94.03	35.05 ± 16.86	< 0.001

Abbreviations are defined in text.
f, female; GCF, gingival crevicular fluid; GI, gingival index; HD, hemodialysis; IL-8, interleukin-8; m, male; PD, pocket depth; PI, plaque index; TNF-α, tumor necrosis factor-α.

Table 2. Hematological characteristics of the study patients

Parameter	Patients (n = 43)	Control group (n = 43)	p-Value
Serum creatinine (μmol/L)	7.81 ± 2.97	1.19 ± 0.08	< 0.001
Serum urea (mmol/L)	147.25 ± 46.86	32.37 ± 5.78	< 0.001
White blood cells (k/μL)	6.05 ± 1.81	7.02 ± 1.30	< 0.001
Hb (g/dL)	10.84 ± 1.21	13.70 ± 0.79	< 0.001
CRP (mg/L)	5.48 ± 6.94	2.89 ± 1.16	0.023
Alb (g/dL)	3.52 ± 0.40	4.09 ± 0.34	< 0.001

Alb, albumin; CRP, C-reactive protein; Hb, hemoglobin.

significantly different between the HD and control groups ($p < 0.001$). The demographic data, periodontal parameters and levels of TNF-α and IL-8 in gingival crevicular fluid for the HD group are shown in Table 1. Periodontal examination revealed gingivitis and periodontitis in 28 and 15 patients, respectively, and there were no significant differences in the amounts of TNF-α or IL-8 in the gingival crevicular fluid between these two groups of patients (Table 4).

Correlations

There were positive correlations between age and PI ($r = 0.420$, $p < 0.001$), GI ($r = 0.395$, $p < 0.001$), and pocket depth ($r = 0.468$, $p < 0.001$). A positive correlation was also observed between the levels of TNF-α and IL-8 in gingival crevicular fluid ($r = 0.494$, $p < 0.001$). We observed positive correlations between TNF-α and PI ($r = 0.642$, $p < 0.001$), TNF-α and GI ($r = 0.565$, $p < 0.001$), TNF-α and pocket depth ($r = 0.522$, $p < 0.001$), IL-8 and PI ($r = 0.402$, $p = 0.002$), IL-8 and GI ($r = 0.396$, $p = 0.002$), and IL-8 and pocket depth ($r = 0.326$, $p = 0.012$). There were negative correlations between albumin and PI ($r = -0.491$, $p < 0.001$), albumin and GI ($r = -0.406$, $p < 0.001$), and albumin and pocket depth ($r = -0.464$, $p < 0.001$). Negative correlations were also found between the GCF levels of TNF-α and IL-8, TNF-α and Hb ($r = -0.745$, $p < 0.001$; $r = -0.285$, $p < 0.05$, respectively) and between the levels of albumin and CRP ($r = -0.467$, $p = 0.002$). There were no significant correlations between laboratory findings and periodontal parameters. Interactions of the multiple variables were determined by regression analysis, the results of which are shown in Table 5.

Discussion

Despite significant technical advances, inflammation is still an important problem in HD patients. The etiology of inflammation in HD patients is variable and includes vascular access infection, bioincompatible membranes, sinusitis, otitis, chronic obstructive lung disease, silent cardiac ischemia, urinary tract infections and periodontal disease (11).

It is important to investigate the complications in HD patients in order to increase their quality of life. Therefore, understanding the physiopathological alterations in periodontal tissues caused by HD, and how these alterations affect the gingival and/or periodontal health may help to improve the oral health status of these patients (16). Several studies have also indicated the presence of higher plaque levels in CRF patients receiving HD therapy (8,17,18). Patients undergoing HD therapy are dependent on health centers because they receive dialysis through a dialysis machine for approximately 4 h several times a week. Al-Wahadni & Al-Omari (8) reported that individuals receiving HD therapy may ignore oral hygiene and other potential problems because of the length of time spent in the dialysis center. Galili *et al.* (18) suggested that patients on HD therapy may be depressed as a result of their severe systemic condition and would therefore show insufficient compliance during dental treatments and neglect oral health care. Marinho *et al.* (19) reported that plaque accumulation is linked to oral hygiene habits and emphasized that these patients' toothbrushing habits were inadequate because of the psychological response to their chronic disease.

Consistent with the reports discussed above, almost none of the HD patients in the present study brushed their teeth regularly and they were unwilling to visit a dentist until problems arose. Therefore, there were significant differences in periodontal parameters between the HD and control groups ($p < 0.001$).

Although the GI values of the HD group were significantly higher than those of the control group in the present study. The low GI score of the HD patients may have been a result of systemic low-grade inflammation and the development and progression of systemic atherosclerosis, leading to impairment in the microcirculation of periodontal tissue. The results of previous studies have been inconsistent in this regard, with several reports of higher (8,17), lower (13,20) and equivalent (21) GI values in HD patients compared with controls. It has been suggested that the uremic state in HD patients may suppress inflammatory reactions in the tissues, which would result in infrequent detection of gingival inflammation in these patients in comparison to healthy controls (3). A previous study in HD patients and healthy controls demonstrated no differences in the evolution of experimental gingivitis in either group (22), indicating that uremia would not retard gingival inflammation in HD

Table 3. Periodontal characteristics of the patients

Parameters	n = 43	Parameters	n = 43	Parameters	n = 43
PI score 1	13 (30.2%)	GI score 1	30 (69.8%)	PD ≥ 2 mm	28 (65.1%)
PI score 2	10 (23.3%)	GI score 2	13 (30.2%)	PD ≥ 3 mm	15 (34.9%)
PI score 3	20 (46.5%)				

GI, gingival index; PD, pocket depth; PI, plaque index.

Table 4. Tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) levels in the gingival crevicular fluid (GCF) of gingivitis and periodontitis groups

Parameters	Gingivitis (n = 28)	Periodontitis (n = 15)	p-Value
GCF TNF-α (pg/mL)	31.20 ± 1.37	31.77 ± 1.45	0.213
GCF IL-8 (pg/mL)	73.31 ± 75.16	78.31 ± 57.01	0.823

patients. Therefore, gingivitis would progress in the same way as in healthy controls and would develop only because of insufficient oral hygiene. We also feel that the significantly increased GI in the HD patient group relative to the control group is associated with patients' poor oral hygiene.

This study was performed to evaluate the relationship between patients undergoing dialysis and the levels of IL-8 and TNF-α in gingival crevicular fluid, which play important roles in the pathogenesis of periodontal disease and in the immune response. The results of this study indicated that the levels of TNF-α and IL-8 in gingival crevicular fluid were significantly higher in HD patients than in the control group. Thus, periodontal parameters were associated with the levels of inflammatory cytokines in the gingival crevicular fluid of HD patients.

As we were unable to find any previous reports regarding gingival crevicular fluid and cytokine levels in HD patients, the extent to which we can discuss these findings is limited. However, Rysz *et al*. (23) reported that the serum levels of IL-1, IL-6, IL-8, and TNF-α were higher in HD patients than in healthy controls. While these researchers investigated serum, we analyzed pocket fluid in the present study. It is interesting that the levels of both IL-8 and TNF-α were higher in the HD patients than in the control group.

Periodontal disease has been suggested to affect cytokine levels (24). In addition, several studies have suggested that periodontitis exerts its clinical effects via the systemic dissemination of locally produced mediators, such as CRP, IL-6, IL-1β and TNF-α (25–28). Engebretson *et al*. (29) reported positive correlations between the IL-8 levels in gingival crevicular fluid and both pocket depth and PI. In agreement with the results reported in the literature, we found that HD patients have high levels of TNF-α (31.77 ± 1.45 pg/mL) and IL-8 (78.31 ± 57.01 pg/mL), and that there are positive correlations between proinflammatory cytokines and periodontal parameters.

The results of periodontal examinations in the present study revealed gingivitis and periodontitis in 28 and 15 patients, respectively. That is, all 43 HD patients had periodontal problems, and we considered this to be related to the high cytokine levels in pocket fluid. However, we found no differences in the levels of TNF-α or IL-8 in the gingival crevicular fluid between HD patients with gingivitis (65%) and those with periodontitis (35%).

We found that the levels of albumin and Hb were lower, while those of CRP, serum creatinine and serum urea were higher, in the HD group than in healthy controls. Kshirsagar *et al*. (30) suggested that there may be a correlation between low albumin levels in HD patients and severity of periodontal disease.

We found negative correlations between albumin and PI (r = −0.491, $p < 0.001$), albumin and GI (r = −0.406, $p < 0.001$) and albumin and pocket depth (r = −0.464, $p < 0.001$). There were also negative correlations between TNF and Hb, TNF and IL-8 in gingival crevicular fluid (r = −0.745, $p < 0.001$; r = −0.285, $p < 0.05$, respectively). Thus, our data supported the findings of the above study.

Inflammation, hypoalbuminemia and anemia were shown to be independent risk factors of morbidity and mortality in HD patients. Several recent studies have confirmed that inflammation, as reflected by elevated levels of serum CRP or proinflammatory cytokines, is a significant independent predictor of mortality in HD (31–33).

The high level of serum CRP, low levels of albumin and Hb, high values for periodontal parameters, and high levels of TNF-α and IL-8 in gingival crevicular fluid, in the present study, highlight the importance of periodontal disease and poor oral hygiene in HD patients, which should be taken into consideration by physicians when designing treatment schedules.

Table 5. Regression analysis of multiple variables with periodontal parameters

Variables	R^2	p-Value
Age, HD vintage, IL-8_{GCF}, TNF-α_{GCF} and PD	0.463	< 0.001
Age, HD vintage, IL-8_{GCF}, TNF-α_{GCF} and PI	0.466	< 0.001
Age, HD vintage, IL-8_{GCF}, TNF-α_{GCF} and GI	0.394	0.001
Age, HD vintage, IL-8_{Serum}, TNF-α_{Serum} and PD	0.445	< 0.001
Age, HD vintage, IL-8_{Serum}, TNF-α_{Serum} and PI	0.449	< 0.001
Age, HD vintage, IL-8_{Serum}, TNF-α_{Serum} and GI	0.386	0.001
HD vintage, urea, creatinine, URR and PD	0.037	0.845
HD vintage, urea, creatinine, URR and PI	0.076	0.572
HD vintage, urea, creatinine, URR and GI	0.058	0.698
HD vintage, Ca, P, ALP, PTH and PD	0.057	0.831
HD vintage, Ca, P, ALP, PTH and PI	0.089	0.640
HD vintage, Ca, P, ALP, PTH and GI	0.052	0.856

ALP, alkaline phosphatase; Ca, calcium; GCF, gingival crevicular fluid; GI, gingival index; HD, hemodialysis; IL-8, interleukin-8; P, phosphorus; PD, pocket depth; PI, plaque index; PTH, parathyroid hormone; TNF-α, tumor necrosis factor-α; URR, urea reduction rate.

Conclusion

The present study revealed that the levels of TNF-α and IL-8 in gingival crevicular fluid were significantly higher in the HD patients than in the controls, and there were strong,

positive correlations between clinical parameters and the levels of both TNF-α and IL-8 in the gingival crevicular fluid of HD patients. Periodontal disease has an adverse effect on serum albumin via elevated gingival cytokine levels, which is an independent risk factor for mortality and morbidity in HD patients. The importance of periodontal examination is reinforced periodically to HD patients by members of the dialysis team. It is very important to maintain an optimal level of oral hygiene in these patients. In order to achieve this, CRF patients should be sent regularly, by the dialysis center, for dental examinations in order to improve their systemic health and quality of life. It is therefore important and necessary for nephrologists to work in cooperation with dentists to monitor the systemic condition of this patient group.

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