Lack of Correlation between Periodontitis and Renal Dysfunction in Systemically Healthy Patients

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ABSTRACT

Objectives: The aim of this study was to assess a suggested association between periodontitis and renal insufficiency by assaying kidney disease markers.

Methods: Variables used to diagnose periodontitis were: (i) probing pocket depth (PPD), (ii) attachment loss (AL), (iii) bleeding on probing (BOP), (iv) plaque index (PI) and (v) extent and severity index. Blood and urine were collected from 60 apparently healthy non-smokers (men and women), consisting of a test group of 30 subjects with periodontitis (age 46±6 yrs) and a control group of 30 healthy subjects (age 43±5 yrs). Kidney function markers (urea, creatinine, uric acid and albumin contents) were measured in the serum and urine. Also, the glomerular filtration rate was estimated from creatinine clearance, from the abbreviated Modification of Diet in Renal Disease formula and from the albumin : creatinine ratio in a 24–h sample of urine.

Results: It was found that the control group had a greater mean number of teeth than the test group and that the two groups also differed in PPD, AL, BOP and PI, all these variables being higher in the test group (P=0.006). For the extent and severity index of both PPD and AL, the test group had much higher medians of both extent and severity than the control group (P=0.001). With regard to kidney function, none of the markers revealed a significant difference between the control and test groups and all measured values fell within the reference intervals.

Conclusions: It is proposed that severe periodontitis is not associated with any alteration in kidney function. (Eur J Dent 2011;5:8-18)

Key words: Kidney function markers; Creatinine clearance; Albumin; Urea; Uric acid.

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INTRODUCTION

Chronic periodontitis, the commonest type of periodontal disease, is defined by the American Academy of Periodontology as an infectious disease resulting in inflammation within of the tissues supporting the teeth, progressive loss of attachment and bone loss. This process leads to pocket formation around the tooth and/or gum recession.[1] This definition is based on a model of infection and host response which, despite the extent of current knowledge on periodontal diseases, is still inadequate for a diagnosis leading to a full classification grounded in the etiology of the disease.[2]

In chronic periodontitis, the bacterial biofilm is assumed to be the etiological agent, implying that this disease is polymicrobial. In the community of bacteria beneath the gums, the gram-negative bacteria are recognized as periodontal pathogens[3] and studies that take into account variables linked to the genetics of both patients and these potential pathogens are likely to give a better insight into the etiology of periodontal disease.[4]

There have been signs that periodontitis may contribute to chronic systemic disease. Thus, some results have revealed an association between periodontitis and atherosclerotic vascular disease.[5-8] The explanation offered for this connection is that periodontal pathogens could circulate in the bloodstream and promote damage to blood vessel endothelium and atherosclerosis.

It is plausible that such damage occurs not only in the endothelia of the heart and brain but also in kidney endothelium. Certainly, it is known that various chronic and acute infections are able to incite an inflammatory response in the kidney called glomerulonephritis.[9] This is a relevant and timely topic because the prevalence of kidney disease is increasing and the majority of patients suffering from kidney disease also suffer from periodontitis.[10] One United States population-based study considers multiple risk factors, including periodontal status, in the identification of individuals at high risk of chronic kidney disease.[11]

With this in mind, some researchers have turned their attention to the relation between periodontitis and renal insufficiency and the results of some work carried out on dogs[12] and on humans[9] confirmed this relation. On the other hand, Yamalik et al[13] observed that bacterial accumulation was similar in systemically healthy individuals with periodontitis and patients with chronic renal failure and periodontitis. Also, no significant differences were observed in mean gingival-periodontal index, probing pocket depth or bleeding index between individuals with and without chronic renal failure.[14] Fisher et al[15] showed that edentulism and periodontitis were independently associated with chronic kidney disease.

Thus, in light of the above controversy and given that the nature of this association is not fully understood, we believe that further investigation is necessary.

One little-used approach to studying this association is to test the hypothesis that periodontitis is correlated with the start of the development of kidney disease. To this end, this study was designed to assess i) the correlation between periodontitis and the levels of kidney function markers in systemically healthy subjects and ii) the distribution of these levels relative to their reference intervals. The classic markers for kidney function[16-19] used in this study were the levels of albumin and non-protein nitrogen compounds in the serum and urine, albumin/urinary creatinine ratio, creatinine clearance, the abbreviated Modification of Diet in Renal Disease formula for predictive estimation of glomerular filtration rates and urinary volume.

MATERIALS AND METHODS
Patient selection

This cross-sectional study (case-control) was conducted from November 2005 to July 2007, after the protocol had been approved (Res.196/05) by the human subject ethics committee of the UNESP School of Dentistry at Araraquara, SP, Brazil, and written informed consent was obtained prior to subject enrollment. The sample size was calculated for α=5%, with 1.0 mm significant difference in clinical measurements between groups, and a standard deviation of 0.8 mm. Therefore, with a sample size of 27 patients, the power of the significance test was calculated to be 85%. A total of 60 subjects were thus included in the study and divided into two groups of 30 participants each. All subjects in both groups were between 32 and 58 years old.

Thirty-six chronic periodontitis subjects (≥14 teeth in the mouth (including third molars), of

which 4 had at least one site with probing pocket depth (PPD) of 3 to 5 mm, and 4 others at least one site with 6 to 10 mm PPD[1]) were recruited from the Periodontal Clinic of the São Paulo State University (UNESP) School of Dentistry at Araraquara, SP, Brazil to form the test group. Six subjects had to be excluded from the group because they did not appear for the collection of biological material, hence, a final of thirty subjects were formed the group. Thirty periodontally healthy volunteers (≥ 14 teeth in the mouth including third molars, bleeding on probing (BOP) at < 30% of periodontal sites with PPD of 1 to 3 mm, only 2 isolated sites with PPD of 4 mm and without BOP, and attachment loss (AL) of 3 mm or more at < 30% of all the sites in the mouth[1,20,21]) from Araraquara city (blood donors and others) not barred by the exclusion criteria were identified and recruited to the control group. Exclusion criteria for both groups were; unfavorable systemic conditions (rheumatic fever or heart problems requiring prophylactic antibiotic treatment and kidney disease), pregnant women, women on hormone replacement therapy or hormonal contraceptives, patients taking steroidal or non-steroidal anti-inflammatory drugs (previous 3 months) or antibiotics (previous 6 months), smokers and subjects showing high-sensitivity C-reactive protein (CRP) above 10 mg/L, these being powerful conditions that could have affected the progression of periodontitis.[22,23]

Both the control and test groups were instructed on how to perform appropriate oral hygiene and were given preventive or curative oral treatment.

The full-mouth periodontal examination (six sites per tooth: mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, disto-lingual) was performed by one calibrated examiner using Williams probe (Hu-Friedy Manufacturing Co., Chicago, USA) of circular cross-section. The following parameters were assessed at the 6 sites around each tooth: (i) PPD, (ii) AL, (iii) BOP and (iv) plaque index (PI). AL was determined from the distance between the cementoenamel junction and the most apical part of the periodontal pocket. BOP indicates the presence (+) or absence (-) of bleeding after probing the pocket. The presence (+) or absence (-) of plaque was observed on the mesial, buccal, distal and lingual faces of each tooth and the PI was calculated. The extent and severity index for periodontitis was calculated from clinical variables (PPD and AL) used to diagnose periodontitis; measurements indicating periodontitis were considered to be AL > 2 mm and PPD > 2 mm. The extent of the disease was taken as the proportion of all sites examined that showed pathological symptoms, both for AL and PPD. Severity was calculated from the scores assigned to AL and PPD at each site: for each mm beyond 2 mm (normal), the score was incremented by 1 and the sum of scores was divided by the number of abnormal sites.[20,21,24]

Laboratory tests

Venous blood samples were taken (8 mL in evacuated tube) from subjects after fasting for 12 h overnight. The 24-hour period of urine collection ended on the morning of the blood collection. The serum and urinary levels of renal function markers (urea, creatinine, uric acid and albumin) were measured[16] and the glomerular filtration rate was estimated from creatinine clearance,[17] from the abbreviated Modification of Diet in Renal Disease formula[18] and from the albumin (mg)/creatinine (g) ratio in the 24-hour urine sample.[19] Serum and urinary urea were determined by enzyme assay[25] in which urea was hydrolyzed by urease to ammonia, which was assayed by measuring the UV absorbance of NADH consumed in the presence of glutamate dehydrogenase. Creatinine was analyzed by the Lustosa-Basques colorimetric method[25] based on the absorbance of colored complexes formed by picrate with creatinine and with interfering compounds, at alkaline pH; when acetic acid is added, the creatinine-picrate complex is destroyed and the difference between the two absorbances is proportional to the amount of creatinine. The uricase assay[25] was used to measure uric acid; the latter is first oxidized while oxygen is converted to hydrogen peroxide, which is then assayed by reaction with peroxidase and a chromogen. Serum albumin was determined by reaction with bromocresol green,[26] which forms a complex with albumin that absorbs at a specific wavelength in the visible. Albuminuria was assessed quantitatively by an immunonephelometric method (N antiserum to human albumin), following the nephelometer kit manufacturer's instructions (Dade-Behring GmbH, Marburg, Germany). Serum and urinary determinations of urea, uric acid, creatinine and albumin were performed in a

Technicon RA-XT autoanalyser (Dublin, Ireland). The reagents for quantitation of serum and urinary uric acid were from Kovalent do Brasil Ltda. (São Gonçalo, Rio de Janeiro), while those for serum albumin and serum and urinary urea and creatinine were from the Labtest Diagnostics S.A. kit (Belo Horizonte, Brazil). Serum and urine samples were analyzed immediately after collection from the subjects.

Statistical analysis

The Chi-square test was used to determine whether a group lay outside or within the reference interval for a given variable, according to the frequency of subjects in each category.

To compare means of quantitative variables in groups, Student´s t-test was used, in conjunction with either a post-hoc Mann-Whitney non-parametric test or a prior log transformation of the data prior to testing. In all statistical tests, significance was accepted when P<.05.

The data for the controls and those for the test group were also separately subjected to multivariate canonical correlation analysis, employing SAS software, in order to reveal correlations between their canonical variables for the periodontal diagnosis variables (number of teeth and values of PPD, AL, BOP and PI) and the kidney function markers (serum albumin and uric acid, serum and urinary creatinine and urea, urinary volume, creatinine clearance, abbreviated Modification of Diet in Renal Disease formula and albumin/creatinine ratio).

RESULTS

The distribution of sexes in the control and test groups was similar: 13 men and 17 women controls and 16 men and 14 women in the test group. There was also no significant difference in age, as the means and standard deviations were 43±5 yrs and 46±6 yrs for the respective groups.

In Table 1, it can be seen that the two groups had different mean numbers of teeth and also differed with respect to PPD, AL, BOP and PI. The PPD and AL results were classified as follows: <3 mm (shallow), 3-5 mm (medium) and ≥6 mm (deep), and the pattern of these classes differed appreciably between the groups; thus, only the test group showed deep pockets. The number of teeth and proportion of shallow pockets (PPD

and AL) among the sites were higher in the control group, while higher values of all other variables were found in the test group (P=0.006). For the extent and severity index of both PPD and AL, the test group had a centre of distribution (median) much higher than that of the control group (P=0.001). The serum and urinary levels of the kidney function indicators in both groups are presented in Table 2. No significant differences were revealed between the two groups in the mean values of any of these variables. The same was true of the glomerular filtration rate-related variables: creatinine clearance (mean), abbreviated Modification of Diet in Renal Disease formula (median) and the urinary albumin/creatinine ratio (median) (Table 3). The absolute and percent frequencies of the renal function indicators found inside and outside their reference intervals in the two groups are displayed in Table 4. Whichever variable is analyzed, it can be seen that there is no evidence that the frequency of results within or outside the reference interval is different in the control and test groups. The same was found for the glomerular filtration rate variables (Table 5). Multivariate canonical correlation analysis, applied to the control group, revealed that larger numbers of teeth and of sites with PPD < 3 mm and AL < 3 mm, and low BOP and PI, are associated with higher levels of serum uric acid, urinary urea and urinary volume, though these levels remained within the respective reference intervals. In addition, a large number of sites with PPD between 3 and 5 mm correlated with higher rates of creatinine clearance. Analyzing the test group, it was found that larger numbers of sites with PPD < 3 mm and low BOP were both associated with higher levels of urinary creatinine and creatinine clearance and lower levels of serum albumin. Also in the test group, it was observed that small numbers of sites with PPD > 6 mm correlated with lower albumin/ creatinine ratios and large numbers of teeth with high serum urea levels. Finally, in the test group, low PI was associated with higher levels of serum and urinary uric acid.

DISCUSSION

In this study, we investigated the possible association between periodontitis and renal insufficiency by assaying kidney disease markers in two groups of subjects, previously diagnosed

with periodontitis (test group) and periodontally healthy (control group).

In the control group shallow pockets were found at 90% of all sites, according to the AL and PPD data. The control group showed AL at around 7.63% of sites and a median severity of 1.0 mm, while in the test group, AL was recorded at 62.44% of sites, with a median severity of 2.58 mm. Thus, an 8 times greater proportion of sites within the mouth was affected by loss of attachment in the test group and it was 158% more severe in the test group than in the control group. Analyzing the results for PPD, the control group had low values while the test group values were higher. With respect to extent, more than 50% of the sites were affected in the test group, while the severity had a median value of 2.25 mm, against 5.23% and 1.00 mm for the control group. Therefore, the two groups were certainly quite distinct, proving that the test group members had severe periodontitis, while the controls did not.

The results demonstrated that patients with periodontitis suffered no alteration in the level of any of the blood or urinary indicators of renal dysfunction, relative to the control group, and furthermore these markers stayed within their normal ranges in both groups, suggesting that severe periodontitis does not affect renal function. These findings were obtained from 8 direct and 3 indirect markers of renal function. Moreover, microalbuminuria, which was similar in the control and test groups, was also within its reference interval in both groups.[32]

Several studies have been published showing correlation between periodontitis and renal dysfunction, some of which involve specific bacterial species. According to Socransky et al,[33] the microorganisms responsible for periodontitis belong to the red complex *(Porphyromonas gingivalis*, *Tanerella forsythia* and *Treponema dentícola)*, while Send et al[34] report that there is considerable evidence that periodontitis-related microorganisms impair blood rheological parameters and thereby contribute significantly to accelerated systemic or local diseases that cause premature death in dialyzed patients.

In the majority of published work on this association, the case group consists of patients with

Table 1. Oral variables assessed in the periodontal diagnosis.

Variable	Control group		Test group		
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Number of teeth	28.0±3.0	28.0 (22.0–32.0)	25.0±4.0	26.0 (14.0–32.0)	*
PPD[a] (% of sites)					
< 3 mm	92.8±5.7	95.0 (79.0–99.4)	46.9±16.1	47.2 (17.5–74.0)	*
3 –5 mm	7.2± 5.7	5.1 (0.6–21.0)	42.8±14.6	44.9 (19.0–76.3)	*
≥ 6 mm	0±0	0 (0–0)	9.8±6.5	9.4 (2.3–28.4)	*
Extent[b] (%)		5.23 (0.60–20.97)		52.82 (26.0–82.5)	†
Severity[c] (mm)		1.00 (1.00–1.40)		2.25 (1.39–3.62)	†
AL[d] (% of sites)					
< 3 mm	89.9±7.0	92.4 (72.0–98.6)	35.1±15.1	37.6 (0.6–57.1)	*
3 –5 mm	9.0±7.0	7.0 (1.0–28.0)	46.0±11.0	46.0 (20.0–65.0)	*
≥ 6 mm	0±0	0 (0-2.0)	17.0±12.0	13.0 (3.0–50.0)	*
Extent[b] (%)		7.63 (1.28–28.00)		62.44 (42.86–99.38)	†
Severity[c] (mm)		1.00 (1.00–2.27)		2.58 (1.45–4.50)	†
BOP (% of sites)	6.0±6.0	4.0 (0–20.0)	51.0±30.0	43.0 (9.0–100.0)	*
PI (% of sites)	16.0±7.0	16.0 (0–33.0)	68.0±34.0	64.0 (0–100.0)	*

PPD: probing pocket depth; AL: attachment loss; BOP: bleeding on probing; PI: plaque index; SD: standard deviation; [a] the greater the PPD, the greater is the risk of periodontitis and inflammation developing, especially if bleeding occurs; [b] % affected among all sites; [c] shows how far beyond 2 mm (normal) was the measured depth or bone loss found in the periodontal diagnosis; [d] best indicator of AL of tooth to bone caused by periodontitis. Significant difference between medians of groups by the Mann-Whitney test: * p = 0.006 and † p=0.001.

proved kidney disease. However, in this approach it is probable that patients have been included whose kidney disease is unrelated to periodontitis, since in most such patients, the illness stems from primary or hereditary syndromes such as Goodpasture's Syndrome, Bergers Disease, Focal Glomerulosclerosis and Membranoproliferative Glomerulonephritis, or more rarely Alport's Syndrome and Autosomal Dominant Polycystic Kidney Disease, or from secondary processes such as Diabetes Mellitus, Polyarteritis Nodosa, Scleroderma, Myeloma Kidney, Sarcoidosis, Amyloidosis, Lupus Nephritis, etc.[35] Thus, the constitution of the test group is critical, since the pathological conditions listed above may interfere with some markers, without necessarily being related to periodontitis.

In addition, for a number of years, reference values have been used for various diseases that do not yet signify the actual disease but are close to the upper limit of the normal range. An example is impaired fasting plasma glucose.[36] The same reasoning could be applied to laboratory assays used as markers for kidney damage, to allow preclinical signs to be detected before the onset of the disease. Thus, by analogy with diabetes, in this study the test and control groups are compared not only with each other but also with kidney dysfunction

Table 2. Serum and urine markers for control subjects and periodontitis patients.

Marker	Group	Mean	SD	Median	Minimum	Maximum
Serum albumin (g/dL)	Control	4.9	0.5	5.0	3.4	5.8
	Test	4.7	0.4	4.7	4.1	5.6
Serum creatinine (mg/dL)	Control	0.9	0.2	0.9	0.6	1.3
	Test	1.0	0.2	1.0	0.7	1.3
Urine creatinine[a] (mg/kg.24h)	Control	18.45	4.30	18.09	11.44	29.02
	Test	17.14	4.75	16.33	10.31	32.99
Serum uric acid (mg/dL)	Control	4.3	1.7	4.1	1.3	8.0
	Test	4.9	2.1	5.0	1.4	8.9
Urine uric acid (mg/24h)	Control	542.2	219.0	520.1	194.6	1089.0
	Test	526.5	222.1	471.1	203.5	1055.0
Serum urea (mg/dL)	Control	30	9	30	12	48
	Test	29	10	28	17	59
Urine urea[a] (g/24h)	Control	25.9	8.0	23.5	13.1	44.6
	Test	24.5	11.0	23.8	9.0	52.8
Urinary volume (mL/24 h)	Control	1600	769	1368	475	3300
	Test	1402	626	1405	490	2700

SD: standard deviation. Statistical analysis: Student's t-test (P<.05); [a]: data transformed into logarithms prior to t-test.

Table 3. Glomerular filtration rate estimates in control subjects and periodontitis.

Variable used	Group	Mean	SD	Median	Minimum	Maximum
Creatinine Clearance[a] (mL/min/1.73m²)	Control	93.68	22.05	90.59	60.01	146.47
	Test	85.28	21.74	79.72	52.40	149.40
MDRD2[b] (mL/min/1.73m²)	Control	81.27	13.28	77.57	62.90	115.43
	Test	78.16	12.03	76.96	62.62	127.40
Albumin/Urinary Creatinine[b] (mg/g)	Control	4.87	3.25	4.25	1.42	16.21
	Test	5.53	4.72	4.36	1.16	20.85

MDRD2: the abbreviated Modification of Diet in Renal Disease formula-equation for predictive estimation of glomerular filtration rates. SD: standard deviation. Statistical analysis: [a]: Student's t-test applied to log-transformed data (P<.05); [b]: Mann-Whitney test (P<.05).

marker reference values. Hence, we would discover whether periodontitis could promote any detectable change in kidney function, even when the marker in question remained within its reference interval, albeit shifted nearer to the upper limit of this range.

Regarding the multivariate canonical correlation analysis, the results for both the control and test groups revealed no more than the other statistical tests, since the correlations found were not relevant. For example, in the control group, the correlation between higher levels of uric acid,

Table 4. Frequency and percentage of control subjects and periodontitis patients whose serum and urine biochemical markers for kidney function are below, within and above their respective reference intervals.

Variable	Classes	Control		Test		RI
		Fr	%	Fr	%	
Serum albumin (g/dL)	within RI	21	70.0	25	83.3	3.5 – 5.2 [25]
	< RI	1	3.3	0	0.0	
	> RI	8	26.7	5	16.7	
Serum Creatinine (mg/dL)	within RI	29	96.7	29	96.7	M: 0.9 – 1.3 [25]
	< RI	1	3.3	1	3.3	W: 0.6 – 1.1
Urinary Creatinine (mg/kg.24hs)	within RI	11	36.7	9	30.0	M: 21 – 26 [26]
	< RI	16	53.3	20	66.7	W: 16 – 22
	> RI	3	10.0	1	3.3	
Serum uric acid (mg/dL)	within RI	23	76.7	21	70.0	M: 3.5 – 7.2 [25]
	< RI	4	13.3	5	16.7	W: 2.6 – 6.0
	> RI	3	10.0	4	13.3	
Urinary uric acid (mg/24h)	within RI	28	93.3	29	96.7	< 1000 [25]
	> RI	2	6.7	1	3.3	
Serum urea (mg/dL)	within RI	25	83.3	25	83.3	15 – 40 [27]
	< RI	1	3.3	0	0	
	> RI	4	13.3	5	16.7	
Urinary urea (g/24hs)	within RI	12	40.0	8	26.7	26 - 43 [27]
	< RI	17	56.7	18	60.0	
	> RI	1	3.3	4	13.3	

M: men; W: women; RI: reference interval; Fr: frequency, i.e. number of subjects in each class with respect to RI. Statistical analysis: c2 test (P<.05). Superscripts in square brackets indicate sources.

Table 5. Frequency and percentage of control subjects and periodontitis patients whose glomerular filtration rate variables are below, within and above their reference intervals.

Variable	Classes	Control		Test		RI
		Fr	%	Fr	%	
Creatinine Clearance (mL/min/1.73m²)	within RI	23	76.7	20	66.7	35 – 44 years: 74 – 138 [25]
	< RI	5	16.7	9	30.0	45 – 54 years: 74 – 129
	> RI	2	6.7	1	3.3	55 – 64 years: 69 – 122
MDRD2 (mL/min/1.73m²)	within RI	20	66.7	20	66.7	35 – 44 years: 74 – 138 [25]
	< RI	10	33.3	10	33.3	45 – 54 years: 74 – 129
						55 – 64 years: 69 – 122
Albumin / Urinary Creatinine (mg/g)	within RI	30	100.0	30	100.0	≤ 30 [28,29]

RI: reference interval; Fr: frequency, i.e. number of subjects in each class with respect to RI. MDRD2: the abbreviated Modification of Diet in Renal Disease formula for predictive estimation of glomerular filtration rate. Statistical analysis: c2 test (P<.05). Superscripts in square brackets indicate sources.

urinary urea, urine volume and creatinine clearance, and large numbers of teeth and a high proportion of sites with PPD<3 mm and between 3 and 5 mm, could be the result of better grinding of food during chewing, leading to enhanced digestion of proteins and nucleoproteins and improved absorption of aminoacids. The same type of explanation could be given for all the apparent correlations in the test group.

Our results are consistent with published data showing that mild, moderate or severe periodontitis was observed in dogs with normal renal function, assessed by serum levels of creatinine and urea and by urine density.[37] Leivadaros et al[38] also found no correlation between the urinary albumin/creatinine ratio and periodontitis, while Taylor et al[39] found no change in urea levels after extraction of all teeth from patients suffering from periodontitis.

In another investigation into whether a link exists between periodontitis and renal function, which employed urinary markers of kidney function, such as volume of urine per 24 h and level of creatinine per 24 hours, and blood markers such as serum creatinine level and creatinine clearance per 24 hours, it was found that the increased incidence of chronic renal failure that occurs with age might enhance the probability of severe periodontitis in the target population.[40] However, those patients were in a far higher age bracket than the present subjects, averaging 77 years of age. Other authors, who also worked with elderly patients, found an association between periodontitis and kidney disease.[41] It is known that old age in itself enables the initiation of periodontitis[6] and thus can be a significant confounding factor in the analysis of the periodontitis - kidney disease relation.

Two methods were used to estimate the glomerular filtration rate, since neither is entirely satisfactory, though creatinine clearance is considered superior. The drawback of creatinine clearance is its dependence on the rigorous collection of all urine for 24 h, while the disadvantage of the predictive abbreviated Modification of Diet in Renal Disease formula is that it is a mathematical model. For independent evidence that the whole urine sample was in fact collected, the albumin/creatinine ratio was measured in a 24 h urine sample,[19] even though the original technique for this determination was based on a single ran-

dom sample.[30] Certainly, under these conditions, the ratio between the two concentrations should stay within the reference interval, and this was observed in 100% of the tests in both groups, indicating that the creatinine clearance results were reliable and thus excluding potentially incomplete urine collection. The values of the glomerular filtration rate, estimated from both creatinine clearance and the abbreviated Modification of Diet in Renal Disease formula, revealed that a high percentage of subjects were within the reference interval in both the control and test groups.

Contradicting our findings, Kshirsagar et al[9] reported an association between periodontitis and both raised serum creatinine levels and a glomerular filtration rate below 60 mL/min per 1.73 m^2, determined by the predictive equation. An association was also observed by Verterinen et al,[42] however, out of all the clinical variables, radiographic results and analyses of saliva constituents, only the albumin level showed significant change.

Taken together, these data indicate that the study model employed can have a considerable influence on the results. An association between periodontitis and kidney disease is often encountered in studies using a population where kidney disease is already diagnosed.[42,43] In these cases, the duration of end-stage renal failure and the type of systemic treatment given to patients affect the association significantly.[43]

A similar association has also been observed in a model used to analyze hemodialysis patients.[44,45] However, even in the study model involving patients with end-stage kidney disease, there is some controversy about the association, since some cases have been reported where periodontal damage was no more severe in such patients.[46] A recent study suggests that the central process leading to premature death lies primarily in an inability to eliminate bacteria and products from the blood, despite hemodialysis.[34]

Shultis et al[47] observed that periodontitis predicts development of overt nephropathy and end-stage kidney disease in individuals with type 2 diabetes. In groups as complex as hemodialysis patients and diabetics, such associations become hard to analyze or discuss.

It is our view that the model used in the present study to assess whether periodontitis is correlated with kidney disease suffers from fewer confound-

ing factors (tobacco, pregnancy, hormonal contraceptives, antibiotics and inflammatory treatment, cardiac and renal problems) than many models found in the literature and it is more reliable than one involving diabetic patients, since the sequelae of diabetes are very complex and generate several kinds of interference, apart from the known tendency of diabetes per se to promote infectious processes.[48]

One limitation of this study is its cross-sectional design. Longitudinal studies are still necessary, either to consolidate the above negative results or perhaps to show that chronic periodontitis is, after all, a risk factor for kidney disease, by detecting subtle changes, within the reference intervals, following treatment for periodontitis.

Another limitation of the present study is that, despite the clearcut statistical difference between the control and test groups, 10% of sites ≥ 6 mm might not have the severity of periodontitis necessary to trigger systemic reactions. In other words, it is unknown how many deep pockets with bleeding on probing and for how long these pockets have to be there before we can measure a systemic reaction. Furthermore, there might be specific bacterial species that trigger stronger systemic responses than others. Such problems make it very difficult to evaluate the real effect of periodontitis on systemic health.

Therefore, the absence of correlation observed between periodontitis and kidney disease in healthy adults leaves room for the possibility that severely impaired kidneys prepare the field for the progression of periodontitis or vice versa.[34]

CONCLUSIONS

Within the limitations of this study and the methodology utilized, it may be suggested from the results that severe periodontitis was not correlated with renal dysfunction in the studied population. Further studies on therapeutic intervention (tests before and after treatment) would make an important contribution to the consolidation of these results.

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