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Effects of non-surgical periodontal therapy on the glomerular filtration rate of the kidney: an exploratory trial

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Abstract

Objective: To determine whether non-surgical periodontal treatment (PT) would exert, in subjects with generalized chronic periodontitis (GCP), some beneficial effect on renal function as indicated by surrogate measures of the glomerular filtration rate (GFR).

Material and Methods: Twenty GCP systemically healthy subjects were treated with PT. Serum samples were collected at baseline and 1 day, 7, 30, 90 and 180 days after treatment. GFR was evaluated using cystatin C, a serum marker and modification of diet in renal disease (MDRD), an equation involving creatinine, urea and albumin. Serum markers of systemic inflammation such as C-reactive protein (CRP), D-dimer, serum amyloid A (SAA) and fibrinogen were also assessed.

Results: The cystatin C level decreased significantly from baseline to the end of the trial ($p < 0.01$). Conversely, MDRD did not vary. A significant inflammatory reaction was produced by PT in the short term. Greater increases were noted for CRP and SAA within 24 h ($p < 0.001$ *versus* baseline), while D-dimer ($p < 0.05$) and fibrinogen ($p < 0.01$) showed mild variations. The values of inflammatory markers were normalized after 30 days.

Conclusions: GFR, as assessed by cystatin C levels, may be positively affected by PT. Because of the exploratory nature of this trial, further research is needed to investigate this preliminary finding.

Key words: Cystatin C; C reactive protein; inflammation; periodontal disease

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Subjects affected by periodontal disease develop an intense local production of pro-inflammatory cytokines that may enter the blood stream as shown by the high levels of inflammatory bio-markers in both gingival tissues and serum (Offenbacher et al. 1981, Hutter et al. 2001). Increasing evidence suggests that this may trigger a systemic acute-phase systemic inflammatory response, characterized by increased levels of acute-phase proteins such as C-reactive protein (CRP) and vascular dysfunction (Wu et al. 2000, Slade et al. 2000, 2003, Joshipura et al. 2004).

Systemic inflammation is closely linked to the onset of atherosclerosis (Ridker et al. 1997). Thus, periodontal treatment (PT) markedly reducing systemic inflammation, as seen by the reduction of the levels of acute-phase markers after therapy (D'Aiuto et al. 2004, 2005a), may determine some important benefits. Moreover, treating periodontitis improves endothelial dysfunction, possibly preventing atherosclerotic-related diseases (Elter et al. 2006, Blum et al. 2007, Tonetti et al. 2007).

Subjects affected by periodontal disease appeared to be associated with some alteration of the function of the kidney as indicated by a significant decrease of the glomerular filtration rate (GFR) as compared with periodontally healthy or gingivitis-affected subjects (Kshirsagar et al. 2005). Indeed, as indicated in a cross-sectional study, subjects with severe periodontal disease are three times more likely to have a low serum albumin concentration than subjects with milder disease

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(Kshirsagar et al. 2007a). Moreover, subjects with impaired renal function show elevated serum antibodies to periodontal pathogens such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans* and *Treponema denticola* (Kshirsagar et al. 2007b).

Recent evidence suggests that GFR may be accurately measured using cystatin C serum levels (Shlipak et al. 2006). Cystatin C is a peptide fragment, a member of the family of the cysteine protease inhibitors, and it is considered a serum marker of renal function in both healthy and diseased patients (Tanaka et al. 2007). Because of its small size, it is filtered by the glomerulus and not secreted but reabsorbed by tubular epithelial cells, where it is subsequently catabolized so that it does not return to the blood flow (Grubb 1992). Thus, it is believed to be an ideal marker of GFR due to the lack of secretion or resorption back into the bloodstream. Conversely, creatinine-based equations are not as precise and sensitive as cystatin C in measuring GFR (Newman et al. 1995) as it has been noticed when compared with modification of diet in renal disease (MDRD) in subjects with kidney disease (Shlipak et al. 2003, Menon et al. 2007).

Thus, on the basis of the systemic effects of periodontal therapy and a possible impairment of the function of the kidney in periodontitis-affected subjects, a study was designed to evaluate, in subjects affected by generalized chronic periodontitis (GCP), through an exploratory intervention trial, the effects of conventional scaling and root planning on renal function as measured by GFR.

Material and Methods

Experimental design

This study was a prospective exploratory monocentric trial with a 6-month follow-up. Ethical approval was obtained from the ethical committee of the faculty of Medicine of the University of Pisa (Italy). The study was conducted according to the principles outlined in the Declaration of Helsinki on experimentation involving human subjects.

Population screening

Potential subjects eligible for this study were identified from the population referred for PT to the Unit of Dentistry and Oral Surgery of the University Hospital of Pisa (Italy). A complete periodontal examination was performed including a medical and dental history, an intra-oral examination and full-mouth periodontal probing. A radiographic examination was undertaken using an ortopantomogram. Every subject who fulfilled the inclusion criteria was provided with detailed information about the study and invited to participate.

To be included, subjects had to show probing pocket depths (PPD) $\geqslant 5$ mm on at least 30% of their total sites. Subjects were excluded if (i) younger than 35 years and older than 70 years; (ii) pregnant or lactating females; (iii) females using contraceptive methods; (iv) suffering from any systemic illnesses including cardiovascular, renal and liver diseases; (v) undergoing any pharmacological treatment within the 3 months before the beginning of the study; and (vi) had already been treated for periodontal disease in the previous 6 months.

Pre-treatment and clinical parameters

Once subjects were included in the study, thorough medical and dental examinations were performed. At this time point (baseline), blood samples were collected and vital signs such as systolic (SBP) and diastolic blood pressure (DBP), cardiac frequency and temperature were measured. All measurements were performed three times and the average was considered as the reference value.

Clinical parameters were assessed using a UNC 15 mm periodontal probe by a calibrated examiner (S. C.) at six sites/tooth excluding third molars. The full-mouth plaque score (FMPS) was measured as the percentage of the total surfaces showing plaque assessed dichotomously on six surfaces per tooth (O'Leary et al. 1972, Tonetti et al. 2002). Similarly, a full-mouth percentage bleeding score (FMBS) was calculated after assessing dichotomously the presence of bleeding on probing (Ainamo & Bay 1975). Full-mouth PPD and recession of the gingival margin (REC) were recorded at the same time, with measurements rounded to the nearest millimetre. Clinical attachment level was calculated as the sum of PPD and REC.

Between baseline and the day of the treatment, all the subjects participated in motivation sessions during which oral hygiene instructions and supragingival debridment were given. Subjects started non-surgical treatment only when a satisfactory plaque control level (FMPS $<20\%$) was achieved. All patients reached this target within 2 weeks.

Blood collection and analysis of the serum markers

Serum samples were collected from a venupuncture in the antecubital fossa at baseline and 1 day, 7, 30, 90 and 180 days after treatment to assess markers of systemic inflammation and renal function. Blood samples were then stored at -20°C. Serum markers of renal function assessed were cystatin C, creatinine and urea. GFR was assessed using the cystatin C level and the equation of MDRD (Levey et al. 1999). Briefly, the equation utilized was

$$\begin{aligned}\text{MDRD GFR} &= 170 \times (\text{serum creatinine concentration})^{-0.999} \\ &\times (\text{age})^{-0.176} \times (0.762 \text{ if patient is female}) \\ &\times (\text{serum urea nitrogen concentration})^{-0.170} \\ &\times (\text{albumin concentration})^{+0.318}\end{aligned}$$

Serum markers of systemic inflammation assessed were CRP, D-dimer, serum amyloid A (SAA) and fibrinogen. Both renal and inflammatory markers were assessed using high-sensitivity tests.

Non-surgical periodontal therapy

A standard cycle of periodontal therapy consisting of oral hygiene instructions, supra- and sub-gingival mechanical instrumentation of the root surface (scaling and root planing) was performed by a single certified periodontist (F. G.) using an ultrasonic instrument with fine tips (EMS, Nyon, Switzerland) and hand instruments. Local anaesthesia was used when needed. Subjects received treatment within 24 h. Two quadrants were instrumented in an afternoon session, whereas the other two were instrumented the following morning.

Re-assessment examinations

Re-assessment visits occurred at 1 day, 7, 30, 90 and 180 days after PT. During these appointments, the examiner recorded any medical history changes and blood samples were collected. Complete dental and periodontal examina-

tions were performed at baseline, 90 and 180 days. At the end of these appointments, a session of supragingival debridement was performed as necessary. No attempt was made to re-instrument residual periodontal pockets.

Data management and statistical analysis

The sample size of this pilot trial was not based on formal power calculations but on logistic considerations. No other study was found in the literature at that time to perform a sample size analysis. All data were entered in an Excel (Microsoft Office 2000) database, proofed for entry errors and analysed using a statistical package (version 11.0, SPSS Inc., Chicago, IL, USA). Variables not normally distributed were logarithmic transformed before being used in parametric comparative analysis.

Continuous normally distributed variables were reported as mean and 95% confidence interval for periodontal data and mean ± SD for the remaining continuous data. Median and inter-quartile ranges were used to describe non-normally distributed and percentage data.

Periodontal parameter variations over time were evaluated using a paired-samples *t*-test, whereas serum marker concentrations were assessed using analysis of variance (ANOVA). Post hoc analysis was performed with least significant difference. Significance was attributed when probability p was <0.05.

Results

Experimental population and periodontal parameters

Thirty-two patients were screened for enrolment. Twenty patients were included as 12 presented systemic pathologies. Nineteen subjects completed the study as one subject dropped out 7 days after treatment for reasons unrelated to the study. The last measurements of this subject were carried forward for statistical analysis.

The experimental population comprised of 40% females, 48 ± 9 years of age, and smokers made up 55% of the sample.

During the study, no major changes in lifestyle issues were reported. Body mass index remained stable throughout the study (Table 1). At baseline, SBP and DBP amounted to 117.6 (DS 12.1) and 77.4 (DS 8.8), respectively. A significant reduction of both SBP and DBP was observed at the end of the trial (ANOVA, $p<0.05$).

At baseline, subjects had the majority of their dentition conserved, but periodontal pocketing was diffuse as more than a third of the total sites showed significant presence of disease (Table 2). Subjects also showed a high level of residual periodontal inflammation, with average bleeding on probing higher than

Table 1. Vital signs before and during follow-up

Parameters	Baseline	1 day	7 days	30 days	90 days	180 days
SBP (mmHg)	117.6 (12.1)	113.3 (9.7)	110.2 (13.0)	110.6 (10.0)	109.5 (8.2)*	109.3 (12.9)*
DBP (mmHg)	77.4 (8.8)	78.0 (9.1)	71.6 (11.2)*	75.6 (9.0)	72.7 (9.7)	72.5 (10.2)*
Body mass index	25.0 (3.0)	25.0 (3.0)	25.0 (3.0)	25.0 (3.0)	26.0 (3.0)	26.0 (3.0)
Cardiac frequency (times per minute)	64.1 (7.5)	68.5 (7.7)	67.3 (6.3)	65.1 (6.9)	66.9 (6.7)	65.9 (5.3)
Temperature (°C)	36.2 (0.3)	36.3 (0.3)	36.0 (0.5)	36.1 (0.2)	36.2 (0.3)	36.2 (0.4)

Data indicate geometric means and SD.
p-value *versus* baseline (ANOVA): *$p<0.05$.
SBP, systolic blood pressure; DBP, diastolic blood pressure; SD, standard deviation.

Table 2. Patient periodontal characteristics

Parameters	Baseline	90 days	180 days	*p*-value of *t*-test from baseline
FMPS	65.0	9.0	9.0	0.001, 0.001
Median (IQ)	(55.2, 74.5)	(6.0, 14.0)	(5.25, 17.75)	
FMBS	53.5	7.0	5.0	0.001, 0.001
Median (IQ)	(44.2, 62.0)	(4.0, 14.0)	(2.5, 8.0)	
Number of pockets ⩾5 mm*	63.3	16.2	15.2	0.001, 0.001
Mean (95% CI)	(49.7, 77.0)	(6.4, 26.1)	(5.9, 24.6)	
Percentage of pockets ⩾5 mm*	36.0	6.0	4.0	0.001, 0.001
Median (IQ)	(30.0, 44.5)	(3.0, 12.0)	(2.0, 12.5)	
PPD (mm)*	4.82	2.98	3.02	0.001, 0.001
Mean (95% CI)	(4.19, 5.45)	(2.97, 3.00)	(3.00, 3.03)	
REC (mm)*	0.43	1.12	1.10	0.001, 0.001
Mean (95% CI)	(0.41, 0.44)	(1.10, 1,13)	(1.08, 1.11)	
CAL (mm)*	5.25	4.10	4.12	0.01, 0.01
Mean (95% CI)	(4.61, 5.89)	(4.08, 4.13)	(4.09, 4.14)	
Number of teeth	25.1	24.7	24.7	NS
Mean (95% CI)	(23.8, 26.5)	(23.3, 26.2)	(23.3, 26.2)	

*Number and percentage of pockets ⩾5 mm, PPD, REC and CAL represent full-mouth averages of each subjects.
FMPS, full-mouth plaque score; FMBS, full-mouth bleeding score; PPD, pocket probing depth; REC, recession; CAL, clinical attachment level; NS, non-significant.

50%. Oral hygiene was, in general, unsatisfactory as FMPS exceeded on average 60%.

PT was successfully conducted (Table 2). Plaque decreased below 10% at both 90 and 180 days (*t*-test, $p<0.001$). Accordingly, FMBS also decreased. In general, subjects showed statistically significant improvements of all periodontal parameters such as the number and percentage of pockets $\geqslant 5$ mm (*t*-test, $p<0.001$). These results were maintained until the end of the trial. No further periodontal improvements were noticed between 90 and 180 days after treatment.

Effect of PT on the GFR and serum parameters of renal function

Table 3 summarizes the GFR and serum markers of renal function before and after treatment. No renal dysfunction was noticed at baseline and no significant differences were observed during the trial in terms of urea, creatinine and GFR according to the MDRD formula. Conversely, cystatin C decreased significantly after 30 days (ANOVA, $p<0.01$).

Effect of PT on systemic inflammation

Our subjects showed a high level of systemic inflammation (Table 4). The CRP baseline values were 3.64 ± 7.23 mg/l. Inflammatory markers showed an evident increase 1 day after treatment. CRP and SAA levels were nearly four and six times the baseline values (ANOVA, $p<0.001$). A significant, although smaller, increase was also noticed for fibrinogen and D-dimer (ANOVA, $p<0.01$ and $p<0.05$, respectively). The values were reverted to baseline values at 7 days for each parameter.

Discussion

This exploratory intervention trial was designed to assess the effect of periodontal non-surgical therapy on markers of kidney functionality. Our results indicate that conventional treatment may reduce an important marker of GFR such as cystatin C in systemically healthy subjects affected by GCP.

To evaluate renal function, we assessed GFR as obtained through serum markers and equations. Our results showed that only cystatin C was significantly decreased after therapy, whereas no alterations of conventional creatinine-based equations were noticed. Cystatin C is believed to be a suitable marker of GFR (Stevens et al. 2008). Ideally, cystatin C is within a range of 0.51–0.98 mg/l (Finney et al. 2000) in the absence of renal disease. During renal pathologies, these values tend to increase; therefore, lower values would suggest a more effective GFR (Fliser & Ritz 2001). Cystatin C levels higher than 1 mg/l substantially increase the risk for progression to kidney disease (Finney et al. 2000). Thus, on the basis of our findings, it may be suggested that periodontal conventional treatment may have beneficial effects on renal function as a more efficient GFR was observed.

Cystatin C is not influenced by age, muscle mass or sex (Laterza et al. 2002), whereas inconsistent data are reported on the impact of cigarette smoking on its levels (Knight et al. 2004, White et al. 2009). Our study also included smokers. However, we did not observe any relevant difference among smokers and non-smokers over the 6-month period (data not shown).

The rationale of the reduction of cystatin C after periodontal therapy may only be speculated. A possible explanation may be related to the positive effects of PT on both systemic inflammatory markers and endothelial function. Indeed, high levels of inflammatory markers may have detrimental effects on renal function (Stuveling et al. 2003, Vidt 2006). This is due to an increased nephron filtration of plasma proteins determining a further release of cytokines in the renal interstitium with subsequent fibroblasts' proliferation, fibrogenesis and ultimately renal scarring contributing to progressive deterioration in function (Remuzzi et al. 2002). Moreover, atherosclerosis may promote the progression of kidney disease (Kasiske 1987) as the mechanisms that cause atherosclerosis may also

Table 3. Changes in the renal parameters throughout the study

Parameters	Baseline	1 day	7 days	30 days	90 days	180 days
MDRD (mL/min./1.73 m^2)	72.8 (9.0)	71.9 (8.6)	70.1 (13.4)	71.6 (9.0)	71.4 (7.5)	68.6 (13.1)
Creatinine (mg/dl)	0.981 (0.129)	0.995 (0.122)	0.981 (0.142)	0.982 (0.113)	0.983 (0.110)	0.995 (0.116)
[Log]Cystatin C (μg/l)	2.928 (0.830)	2.907 (0.336)	2.896 (0.645)	2.873 (0.050)**	2.886 (0.051)*	2.870 (0.055)**
[Log]Urea (mg/dl)	1.53 (0.10)	1.51 (0.12)	1.53 (0.10)	1.54 (0.09)	1.54 (0.08)	1.51 (0.08)

Data indicate geometric means and SD.
p-value *versus* baseline (ANOVA): *$p<0.05$; **$p<0.01$.
MDRD, modification of diet in renal disease; SD, standard deviation.

Table 4. Concentrations of serum inflammatory markers

Parameters	Baseline	1 day	7 days	30 days	90 days	180 days
Fibrinogen (mg/dl)	288.9 (69.4)	357.4 (72.2)**	308.8 (59.5)	257.7 (57.8)	258.1 (53.7)	262.9 (54.1)
[Log]CRP (μg/l)	2.27 (0.43)	3.05 (0.22)***	2.50 (0.20)*	2.20 (0.40)	2.10 (0.24)	2.12 (0.27)
D-dimer (mg/l)	0.06 (0.10)	0.12 (0.15)*	0.06 (0.04)	0.06 (0.07)	0.05 (0.05)	0.08 (0.19)
[Log]SAA (μg/ml)	0.82 (0.35)	1.50 (0.39)***	0.81 (0.46)	0.65 (0.36)	0.61 (0.29)	0.67 (0.37)

Data indicate geometric means and SD.
p-value *versus* baseline (ANOVA): *$p<0.05$; **$p<0.01$; ***$p<0.001$.
CRP, C-reactive protein; SAA, serum amyloid A; SD, standard deviation.

be involved in glomerulosclerosis (Diamond 1991). Mesangial cells and vascular smooth cells respond in a similar manner to inflammatory and prothrombotic factors. Indeed, renal insufficiency is associated with higher levels of inflammatory markers, partly explaining the increased risk of cardiovascular disease among these subjects (Shlipak et al. 2003). Inflammatory and prothrombotic markers are predictors of a change of renal function in elderly individuals (Fried et al. 2003, 2004). Therefore, there may exist a positive feedback loop in which a reduction of renal function leads to an increase of inflammatory markers, which then leads to progression of kidney disease and a further increase of inflammatory markers (Fried et al. 2004). Thus, the reduction of the inflammation and the consequent improvement of endothelial function (Seinost et al. 2005) associated with PT may also have an impact on the kidney microcirculation with a subsequent more effective filtration. Interestingly, it has been suggested that periodontitis may influence the occurrence of early organ alterations in certain conditions, such as diabetes, as kidney hypertrophy and increased glomerular volume were observed in prediabetic rats with periodontitis (Pontes Andersen et al. 2008).

Treatment of periodontitis may result systemically in a 2-fold action. On the one hand, in the short term, PT may result in a significant acute trauma (Kweider et al. 1993, Ebersole et al. 1997, Loos et al. 2000, Hutter et al. 2001, Noack et al. 2001, D'Aiuto et al. 2005b). Accordingly, in this study, inflammatory markers showed a significant increase 24 h after treatment. On the other, control of periodontal infection with intensive therapy may increase endothelial function and may reduce systemic inflammatory markers acting on the risk of serious diseases as has already been suggested (D'Aiuto et al. 2005a, b). In our study, a trend towards reduction of systemic inflammation was noticed despite being not statistically significant. There is overwhelming evidence showing that periodontitis patients present higher levels of CRP (Paraskevas et al. 2008). The variability, however, of the response to PT has already been reported in studies with a larger sample size and a controlled study design (Ide et al 2003, Tonetti et al. 2007). There are a number of factors that may affect CRP levels such as obesity, exercise, diet and smoking, which might have played a role in our study. Because of the limited numbers, we were unable to perform multivariate statistics. However, we do not exclude that a longer patient follow-up period might have provided more data on the kinetics of blood markers of systemic inflammation.

Interestingly, SBP and DBP reduced after treatment. A positive effect on blood pressure was already noticed (D'Aiuto et al. 2006). This finding may be due to the decrease of patient anxiety during treatment and, most probably, due to the effect of PT on vascular function (Seinost et al. 2005).

To conclude, on the basis of this exploratory trial, an effect, although mild, on GFR has been noted after therapy. Nonetheless, further studies with larger cohorts and an experimental design (randomized controlled trials) are needed to confirm and to investigate the significance of this preliminary finding.

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Clinical Relevance

Scientific rationale for the study: PT is able to reduce acute-phase proteins levels and systemic inflammatory markers, which are involved in the progression of renal disease. Thus, PT should also be able to exert beneficial effects on the function of the kidney.

Principal findings: Cystatin C, a marker of GFR, decreases after non-surgical periodontal therapy.

Practical implications: As increased levels of cystatin C are associated with renal impairment, PT may have some beneficial effects on renal function.