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Increased levels of circulating endothelial progenitor cells in subjects with moderate to severe chronic periodontitis

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Abstract

Aim: Emerging evidence shows that periodontal disease is associated with endothelial dysfunction. The purpose of this study was to determine the association between chronic periodontitis (CP) and circulating endothelial progenitor cells (EPC).

Materials and Methods: Eighty-six non-smoking subjects (36 males and 50 females, aged 35–80 years) were recruited, including 23 subjects with no or mild CP and 63 subjects with moderate to severe CP. The levels of circulating EPC were quantitatively determined by fluorescence-activated cell analysis, including $CD34^+$/kinase insert domain-containing receptor $(KDR)^+$ (more mature EPC) and $CD133^+/KDR^+$ (less mature EPC). Periodontal conditions, the intima–media thickness of carotid arteries and circulating biomarkers were examined.

Results: Subjects with moderate to severe CP exhibited an increased risk of high EPC count, compared with those with no or mild CP: $CD34^+/KDR^+$ EPC [odds ratio (OR) = 9.5, 95% confidence interval (95% CI) 1.5–61.0, $p = 0.018$; $CD133^+/KDR^+$ EPC, OR = 4.6, 95% CI 1.1–19.5, $p = 0.039$]. C-reactive protein was significantly associated with high $CD34^+/KDR^+$ EPC count and age was inversely related with high EPC count. Age, gender and $CD34^+/KDR^+$ EPC were independent variables of increased carotid intima–media thickness ($p < 0.05$).

Conclusion: This study shows for the first time that moderate to severe CP is associated with an increased level of circulating EPC.

Key words: C-reactive protein; endothelial function; endothelial progenitor cells; periodontitis

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Periodontal diseases, including gingivitis and periodontitis, are among the most commonly occurring infections in humans. They are initiated by pathogenic plaque biofilms and periodontitis is characterized by bacteria-induced inflammatory destruction of tooth-supporting structures and alveolar bone. They are unique and silent infections with potentially profound effects on general health as well (Jin 2008). Emerging evidence suggests that periodontal disease may be associated with cardiovascular disease (CVD) by contributing to an increased level of systemic inflammation. Periodontitis is associated with a cluster of systemic biomarkers of inflammation including C-reactive protein (CRP) (D'Aiuto et al. 2004, Joshipura et al. 2004, Montebugnoli et al. 2004, Buhlin et al. 2009) and interleukin-6 (IL-6) (Loos et al. 2000, Buhlin et al. 2003, D'Aiuto et al. 2004), high- and low-density lipoprotein cholesterols (Katz et al. 2001, 2002, Buhlin et al. 2003, Montebugnoli et al. 2004), von Willebrand factor, tissue plasminogen activators (Joshipura et al. 2004, Montebugnoli et al. 2004) and levels of antibodies induced by periodontal pathogens (Schenkein et al. 1999, Pussinen et al. 2003). It has recently been reported that there may be a great

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heterogeneity of systemic inflammatory responses to periodontal therapy among subjects with severe periodontitis and the determinants of the inconsistent responses across subjects remain unclear (Behle et al. 2009).

Endothelial dysfunction has been recognized as an early marker of pre-clinical CVD (Faulx et al. 2003, Gokce et al. 2003). Brachial artery flow-mediated dilation (FMD) is a non-invasive measurement of endothelial dysfunction (Faulx et al. 2003). In recent years, circulating endothelial progenitor cells (EPC), a subtype of bone marrow-derived stem cells, have received much attention (Asahara et al. 1997, Takahashi et al. 1999, Hristov et al. 2003). They can express surface antigens of both haematopoietic stem cells and endothelial cells (Hristov et al. 2003), and participate in endothelial repair of vasculature and maintenance of vascular integrity (Asahara et al. 1997, Takahashi et al. 1999). The commonly used markers for EPC identification include CD34, CD133 and kinase insert domain-containing receptor (KDR). CD34 and CD133 are antigens of hematopoietic stem cells, and KDR is a marker of endothelial cells (Fadini et al. 2006). $CD34^-/CD133^+/KDR^+$ reflects less mature EPC and $CD34^+/CD133^-/KDR^+$ reflects more mature EPC (Wojakowski et al. 2008). The number and function of EPC have been significantly related to CVD, and this association may reflect the host capacity to repair injured vasculature (Kunz et al. 2006). Indeed, the number of EPC has been proposed as a surrogate marker for endothelial dysfunction and cumulative cardiovascular risk (Hill et al. 2003), and shown to be correlated with the endothelial function as assessed by FMD (Hill et al. 2003, Wojakowski et al. 2008).

It has been reported that control of periodontal infection through periodontal treatment could reduce serum levels of certain biomarkers related with atherosclerosis including CRP and IL-6 (Fokkema et al. 2003, D'Aiuto et al. 2004, 2006 Pussinen et al. 2004, Montebugnoli et al. 2005), and significantly improve endothelial function assessed by both FMD (Mercanoglu et al. 2004, Seinost et al. 2005, Elter et al. 2006, Blum et al. 2007) and carotid intima–media thickness (IMT) (Piconi et al. 2009). A recent randomized-controlled clinical trial confirmed that intensive periodontal treatment resulted in a temporary increase of serum levels of CRP and IL-6, while 6 months after the treatment, endothelial function improved significantly (Tonetti et al. 2007). However, the relevant mechanism remains to be clarified. The aim of this study was therefore to investigate the potential association between chronic periodontitis (CP) and circulating EPC.

Materials and Methods

Subjects

Eighty-six Chinese adults (36 males and 50 females, aged 35–80 years), who were recruited from a health screening programme at the Department of Medicine, Queen Mary Hospital, The University of Hong Kong, were included in the study between 1 November 2007 and 30 April 2008. All subjects had neither symptoms of angina nor a history of CVD, diabetes mellitus or major depression, and they had a coronary calcium score of <10 as detected by multislice cardiac-computed tomography. Subjects with any of the following conditions were excluded from the study: documented CVD including stroke, coronary artery diseases, valvular heart diseases, cardiomyopathy, heart failure and cardiac arrhythmias, neoplastic; systemic illnesses; recent infections, febrile illness or inflammatory disease; use of antibiotics, anti-inflammatory or immunosuppressant agents in the last 3 months; periodontal therapy in the last 6 months; and former or current smokers. This study was approved by the Institutional Review Board of The University of Hong Kong/Hospital Authority Hong Kong West Cluster. Oral and written informed consent was obtained from all participants before the study.

All the subjects' baseline demographic and clinical characteristics, blood sampling and vascular ultrasound were obtained prospectively on the same day. Fasting blood samples were obtained from all subjects to determine serum creatinine, glucose and lipid levels. CRP level was measured using a particle-enhanced immunoturbidimetric assay (Roche Diagnostics, Mannheim, Germany) with a chemistry analyser (Hitachi 747 Analyzer, Boehringer Mannheim, Mannheim, Germany).

Periodontal examination

Clinical parameters were assessed blindly by a single examiner (X. L.) in the Prince Philip Dental Hospital, Hong Kong, and a calibration exercise was performed accordingly with a good intra-examiner reproducibility (κ value $= 0.762$). The subjects underwent a full-mouth, comprehensive periodontal examination at six sites per tooth excluding the third molars, including the number of missing teeth, presence or absence of plaque, bleeding on probing, probing depth (PD) and gingival recession (GR). GR data were recorded as follows: when the free gingival margin (FGM) was apical to the cementoenamel junction (CEJ), the distance from the CEJ to the FGM was recorded as a plus (+) value; when the FGM was at or coronal to the CEJ, the distance was recorded as a zero or minus (−) value. Interproximal clinical attachment loss (CAL) was calculated as the sum of the PD and GR values.

Moderate to severe CP was defined if subjects fulfilled any of the following criteria: (i) more than six sites with PD ≥ 4 mm; (ii) over 25% of sites with interproximal CAL ≥ 5 mm; and (iii) more than eight missing teeth due to CP excluding the third molars. Those subjects who did not fulfill any of the above three criteria were regarded as experiencing no or mild CP.

Flow cytometry

The circulating EPC were defined by the expression of surface markers $CD34^+/KDR^+$ and $CD133^+/KDR^+$, and their counts were measured by fluorescence-activated cell analysis of peripheral blood sample as described previously (Lau et al. 2007). In brief, 100 μl of peripheral blood were incubated with a phycoerythrin-conjugated monoclonal antibody against human KDR (Sigma, St. Louis, MO, USA), followed by fluorescein isothiocyanate (FITC)-conjugated CD34 and CD133 antibodies (Beckman Coulter, Fullerton, CA, USA). FITC-labelled anti-human CD45 antibody was used for differential gating during flow analysis. FITC-labelled IgG1a (Beckman Coulter) and phycoerythrin-labelled IgG2b (Becton Dickinson, Franklin Lakes, NJ, USA) served as the isotypic control for colour compensation. Analysis was performed with an automated fluorescence-activated cell counter (Elite, Beckman Coulter), in

which 1,000,000 events were counted. The absolute cell count of all the measured components per 1,000,000 events in the lymphocyte gate was calculated.

Image analysis of carotid atherosclerosis

The carotid arteries were evaluated by an experienced operator, who was blinded to the periodontal condition of each subject. The detailed method was described previously (Lau et al. 2007). The mean maximum IMT was calculated by averaging the values of maximum IMT measured from 12 preselected segments in the carotid arteries. Plaque thickness was incorporated in the IMT measurement.

Statistical analysis

The clinical parameters were calculated for each subject and the normality of various variables was tested before analysis. EPC count was transformed into ordinal variables (low: first to third quartile, or high: fourth quartile) using quartiles. The median of IMT in the study cohort was used as the threshold to classify as thick IMT or not. Parametric or non-parametric analysis was used as appropriate. Logistic regression was used to identify the independent variables related with high levels of $CD34^+/KDR^+$, $CD133^+/KDR^+$ EPC and thick IMT. p-value <0.05 and >0.10 were considered statistically significant and non-significant, respectively. All statistical analysis was performed using a software programme (SPSS 14.0, SPSS Inc., Chicago, IL, USA).

Results

Using a normality test, EPC count of the 86 subjects was not normally distributed, ranging from 18.0 to 1992.0 cells/μl for $CD34^+/KDR^+$ EPC; and 8.0 to 515.0 cells/μl for $CD133^+/KDR^+$ EPC. Accordingly, the EPC levels were divided into low and high count by quartiles (Table 1).

Subjects with no or mild CP ($n = 23$) were younger (52.5 ± 9.0 years) than those ($n = 63$) with moderate to severe CP (58.7 ± 10.1), $p = 0.011$. Moderate to severe CP was associated with thick IMT (thicker than the median, i.e., 0.8 mm) and high $CD34^+/KDR^+$ EPC count ($\geq$ 75th percentile), $p<0.05$. There were no significant differences in other demographic and circulating biomarkers between the two groups (Table 2).

Table 1. EPC count (cells/μl) in the 86 subjects investigated

Statistics	CD34+/KDR+	$CD133^+/KDR^+$
Mean	264.2	90.2
SD	342.7	83.2
Median	140.0	68.0
SE	37.4	9.1
Range	18.0–1992.0	8.0–515.0
Low count (first to third quartile)	$\leqslant$305.4	$\leqslant$104.4
High count (fourth quartile)	$\geqslant$305.5	$\geqslant$104.5

EPC, endothelial progenitor cells; KDR, kinase-insert domain-containing receptor.

Logistic regression analyses showed that compared with the subjects with no or mild CP, those with moderate to severe CP had higher levels of $CD34^+/KDR^+$ EPC, with an odds ratio (OR) of 9.5 [95% confidence interval (95% CI) 1.5–61.0, $p = 0.018$] (Table 3). Age was negatively associated with high EPC count (OR = 0.9, 95% CI 0.8–1.0, $p = 0.047$), while CRP level was significantly correlated with an increased risk of high EPC count (OR = 1.7, 95% CI 1.2–2.4, $p = 0.005$). Regarding the levels of $CD133^+/KDR^+$ EPC, age was inversely related with high EPC count (OR = 0.9, 95% CI 0.8–0.98, $p = 0.013$), and subjects with moderate to severe CP had an increased risk of a high EPC count (OR = 4.6, 95% CI 1.1–19.5, $p = 0.039$) (Table 4).

Univariable analysis showed that age, gender, education level, the waist–hip ratio and moderate-to-severe periodontits were significantly related with thick IMT. In the multivariable analysis, age, gender and $CD34^+/KDR^+$ EPC were the independent variables of thick IMT ($p<0.05$) (Table 5).

Discussion

In the present study, it was interesting to note that subjects with moderate to severe CP showed an increased risk of high EPC level. Recent evidence shows that systemic inflammation may affect EPC levels. In patients with bacterial pneumonia, inflammatory stimuli could significantly increase the EPC levels (Yamada et al. 2005). An administration of bacterial lipopolysaccharide to murine lungs was able to increase EPC level markedly (Yamada et al. 2004). It could therefore be hypothesized that relatively high levels of EPC may reflect an altered endothelial function that might to some extent be affected by an increased level of systemic inflammation arising from uncontrolled periodontal infections and other unidentified/unknown conditions in the current study population. Further study is needed to confirm this hypothesis.

The present study showed a positive association between CRP level and EPC count in systemically healthy Chinese subjects. Although no significant difference was found in CRP levels between the subjects with moderate to severe CP and those with no or mild CP, CRP count may provide a biological plausibility for the linkage of periodontal infection with EPC levels. Current evidence shows that periodontal disease is a chronic, low-grade inflammation that could significantly increase the systemic level of inflammation (D'Aiuto et al. 2004, Joshipura et al. 2004, Montebugnoli et al. 2004) measured by CRP and IL-6; and periodontal treatment could significantly reduce the levels of these bio-markers (Fokkema et al. 2003, Pussinen et al. 2004, Montebugnoli et al. 2005, D'Aiuto et al. 2006). Furthermore, although intensive periodontal treatment resulted in a temporary increase of serum levels of CRP and IL-6, endothelial function improved significantly 6 months after the periodontal treatment (Tonetti et al. 2007). Recent studies on bacterial pneumonia and ours in the present study support the hypothesis that systemic inflammation may increase EPC levels (Yamada et al. 2004, 2005). The interrelation of CP, CRP and EPC may be a complex one and further studies with more appropriate measurements of the burden of periodontal infection and inflammation are highly warranted to clarify the current findings.

The present study on a Chinese cohort with systemically healthy condition showed a positive association between CRP and EPC, while CRP was inversely associated with EPC

Table 2. Demographic and clinical characteristics of the study population with different periodontal conditions

Variables [mean ± SD or median (range)]	No or mild periodontitis ($N = 23$)	Moderate to severe periodontitis ($N = 63$)	*p*-value
Age (years)	52.5 ± 9.0	58.7 ± 10.1	0.011
Male, no. (%)	7 (30.4)	29 (46.0)	NS
Education level, no. (%)			0.055
Low	3 (13.0)	23 (36.5)	
Middle	6 (26.1)	18 (28.6)	
High	14 (60.9)	22 (34.9)	
BMI (kg/m^2)	23.9 ± 3.8	23.8 ± 3.7	NS
Waist–hip ratio	0.86 ± 0.09	0.88 ± 0.08	NS
Mean DBP (mmHg)	70.6 ± 7.8	74.3 ± 9.7	NS
Mean SBP (mmHg)	118.8 ± 14.7	121.8 ± 13.1	NS
Total cholesterol (mmol/l)	5.0 ± 0.7	4.9 ± 0.7	NS
Triglycerides (mmol/l)	1.1 (0.6–2.6)	1.2 (0.5–6.6)	NS
LDL (mmol/l)	2.9 ± 0.6	2.9 ± 0.7	NS
HDL (mmol/l)	1.4 (0.8–2.6)	1.5 (0.8–3.0)	NS
Serum creatinine (mmol/l)	71.7 ± 13.0	73.3 ± 17.1	NS
CRP (mg/l)	1.0 (< 1.0–8.0)	1.0 (< 1.0–8.0)	NS
⩽2 mg/l [no. (%)]	18 (78.3)	51 (81.0)	NS
⩾3 mg/l [no. (%)]	5 (21.7)	12 (19.0)	
IMT (mm)	0.75 ± 0.15	0.83 ± 0.15	0.039
⩽0.8 mm [no. (%)]	17 (73.9)	27 (42.9)	0.011
>0.8 mm [no. (%)]	6 (26.1)	36 (57.1)	
CD34$^+$/KDR$^+$ EPC (cells/μl)	165.0 (54.0–372.0)	124.0 (18.0–1992.0)	NS
Low count [no. (%)]	21 (91.3)	43 (68.3)	0.03
High count [no. (%)]	2 (8.7)	20 (31.7)	
CD133$^+$/KDR$^+$ EPC (cells/μl)	77.0 (22.0–515.0)	69.0 (80–389.0)	NS
Low count [no. (%)]	20 (87.0)	44 (69.8)	NS
High count [no. (%)]	3 (13.0)	19 (30.2)	

Table 3. Logistic regression on the relationship of risk variables with high CD34$^+$/KDR$^+$ EPC count (⩾75th percentile)

Risk variables	OR	95% CI	*p*-value
Age (years)	0.9	0.8–1.0	0.047
CRP (mg/l)	1.7	1.2–2.4	0.005
Moderate to severe periodontitis*	9.5	1.5–61.0	0.018

*Compared with subjects with no or mild periodontitis.
CRP, C-reactive protein; KDR, kinase-insert domain-containing receptor; EPC, endothelial progenitor cells; OR, odds ratio; CI, confidence interval.

Table 4. Logistic regression on the relationship of risk variables with high CD133$^+$/KDR$^+$ EPC count (⩾75th percentile)

Risk variables	OR	95% CI	*p*-value
Age (years)	0.9	0.8–0.98	0.013
Moderate to severe periodontitis*	4.6	1.1–19.5	0.039

*Compared with subjects with no or mild periodontitis.
KDR, kinase-insert domain-containing receptor; EPC, endothelial progenitor cells; OR, odds ratio; CI, confidence interval.

count in another group of Chinese patients with coronary artery disease (Wang et al. 2007). In addition, our study also showed that CD34$^+$/KDR$^+$ EPC count was positively associated with thick-carotid IMT, which was inconsistent with the results obtained in patients with stroke (Lau et al. 2007). The different systemic conditions of the study population may account for the inconsistencies observed on the relationship of CRP, EPC and IMT. CRP could directly attenuate EPC survival, differentiation and function (Verma et al. 2004, Fujii et al. 2006). It could be hypothesized that in healthy subjects, the host may produce more EPC from the bone marrow to compensate the dysfunction of EPC or to contribute to the potential of endothelial repair during atherosclerosis. However, for stroke patients or those with coronary artery disease, this compensation to some extent may be compromised and EPC levels may decrease accordingly.

A recent study, has confirmed that periodontal treatment can significantly improve endothelial function assessed by FMD (Tonetti et al. 2007), while the mechanism remained unclear. The present observation on the association of periodontitis with EPC level may be a clue for further exploring the relationship between periodontal infection, systemic inflammation and endothelial function. In addition, it has been reported that periodontitis is associated with an increased carotid IMT (Beck et al. 2001, 2005, Cairo et al. 2008), and age was inversely related with EPC levels (Wang et al. 2007, Jie et al. 2009). The present findings are basically consistent with these studies.

In the present study, the EPC count presented with a wide range among the 86 subjects is consistent with a previous study (Lau et al. 2007). Emerging evidence shows that various conditions or diseases (e.g., high level of CRP, age and smoking, diabetes, hypertension and hyperlipidaemia) may account for a relatively low level of EPC count, while stroke, pregnancy and bacterial pneu-

Table 5. Univariable and multivariable model of the relationship between risk variables and thick carotid IMT (>0.8 mm)

Risk variables	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (years)	1.1 (1.0–0.1.12)	0.004	1.1 (1.0–1.2)	0.001
Male *versus* female	2.9 (1.2–7.0)	0.019	4.3 (1.5–12.2)	0.006
Education level*	0.6 (0.4–0.9)	0.046	0.9 (0.4–1.8)	0.751
BMI (kg/m^2)	1.1 (0.9–1.2)	0.345		
Waist–hip ratio	1.3×10^5 ($25.8–6.5 \times 10^6$)	0.003	46.9 ($0.01–3.3 \times 10^5$)	0.395
Mean DBP (mmHg)	1.0 (0.9–1.1)	0.168		
Mean SBP (mmHg)	1.0 (0.9–1.1)	0.151		
Total cholesterol (mmol/l)	2.1 (0.9–4.6)	0.059	1.8 (0.8–4.1)	0.168
Triglycerides (mmol/l)	1.3 (0.7–2.4)	0.373		
LDL (mmol/l)	1.2 (0.6–2.2)	0.623		
HDL (mmol/l)	0.5 (0.2–1.4)	0.203		
Serum creatinine (mmol/l)	1.0 (0.9–1.1)	0.241		
CRP (mg/l)	1.2 (0.9–1.6)	0.117		
CD34$^+$/KDR$^+$ EPC (cells/μl)	1.0 (>1.0–1.003)	0.09	1.002 (>1.0–1.004)	0.024
CD133$^+$/KDR$^+$ EPC (cells/μl)	1.0 (0.99–1.006)	0.824		
Moderate to severe periodontitis	3.8 (1.3–10.9)	0.014	2.2 (0.7–7.5)	0.198

*Categorical data.

CRP, C-reactive protein; KDR, kinase-insert domain-containing receptor; EPC, endothelial progenitor cells; OR, odds ratio; CI, confidence interval.

monia may contribute to an increased level of EPC count (Wojakowski et al. 2008). Therefore, it was premature to assume it is ''good or bad'' only based upon the number of EPC, because both EPC level and function are equally important. In addition to the different methods and antigenic profile used to assess EPC count, currently no information is available on the normal level and range of EPC count. Consequently, the present study used a statistical method to transform EPC count into ordinal variables using quartiles.

Currently, there is no consensus about the criteria or definition to categorize the extent or severity of periodontitis (Beck et al. 2001). Various methods, or even more than one method conducted by the same research group were applied. Referring to other studies (Beck et al. 2001, Amar et al. 2003, Tonetti et al. 2007, Tu et al. 2007), the present study used an alternative and modified definition of moderate to severe CP by the fulfillment of any of the following criteria: (i) ''more than six sites with PD ≥ 4 mm'' modified from the case definition for periodontitis (Page & Eke 2007), shows there are currently at least two teeth with periodontal destruction; (ii) ''more than 25% of sites with interproximal attachment loss ≥ 5 mm'' may reflect an extensive infectious burden of periodontitis on systemic effects, while excluding the buccal GR due to trauma or overzealous brushing (Beck et al. 2001, Kshirsagar et al. 2007); (iii) ''more than eight missing teeth'' may be an appropriate categorical variable to show the association of oral health conditions with CVD mortality, instead of the number of missing teeth used as a continuous variable (Tu et al. 2007). From periodontal assessment points of view, tooth loss principally due to multiple tooth extraction or natural exfoliation may significantly affect the assessments of periodontal indices (Corbet 2007), and an increase of tooth retention in the elderly could result in the remaining teeth with more severe periodontitis (Joshi et al. 1996). Consequently, the present study selected PD, proximal attachment loss and number of missing teeth as appropriate measurements of moderate to severe CP experience, and utilized them for case definition. On the other hand, in periodontal medicine when periodontitis is assessed as an exposure or a potential risk factor for systemic conditions or diseases, it is probably more relevant and objective to examine the relationship of periodontal infection and the resultant inflammation to systemic conditions or diseases, such as the measurement of the antibodies to periodontal pathogens in circulation concurrently, named a tailored-multimodal clinico-laboratory approach (Williams & Paquette 2003, Abbas et al. 2006). Further study should take this point for consideration.

The present study, was a cross-sectional investigation with a relatively small sample size, especially for the subjects with no or mild CP. In the study, EPC count was the main outcome measure, while its functional activity was not assessed. In addition, uncontrolled periodontitis may be only one of several possible factors accounting for the increased levels of circulating EPC in the present study subjects, and other unknown conditions or confounders are warranted for further investigation. Within the limitation of the study, it was concluded that moderate to severe CP may be associated with an increased level of circulating EPC. Further study is warranted to clarify the potential mechanisms of the effects of periodontal infections and the resultant inflammation on EPC activity, and the relevant clinical implications.

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Clinical Relevance

Scientific rationale for the study: EPC are circulating stem cells originating from the bone marrow, which actively participate in endothelial repair of vasculature. This study was to investigate the association of EPC with CP.

Principal findings: Subjects with moderate to severe CP exhibited higher EPC counts compared with control subjects. Age, gender and $CD34^+/KDR^+$ EPC were independent variables of thick carotid IMT (>0.8 mm).

Practical implications: The present study implies that high levels of EPC may reflect an altered endothelial function that might to some extent be affected by an increased systemic inflammation arising from uncontrolled periodontal infections. Further study is warranted to clarify the underlying mechanisms and interventional implications in the management of periodontal patients.