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Relationship between markers of metabolic control and inflammation on severity of periodontal disease in patients with diabetes mellitus

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Abstract

Aim: The aim of this study was to investigate the relationship between markers of metabolic control and inflammation and periodontal disease parameters in patients with diabetes.

Material & Methods: One hundred and eighty one adult patients with diabetes attending treatment at two diabetes centres were invited to participate in the study. Periodontal examination included full-mouth assessment for probing depths and bleeding on probing (BOP). Blood analyses were carried out for glycated haemoglobin, (HbA1c), high-sensitivity C reactive protein, (hsCRP) and lipid profile comprising total cholesterol, low-density lipoprotein cholesterol (LDL chol), high-density lipoprotein cholesterol (HDL chol) and triglycerides.

Results: Upon multivariate analysis, periodontal disease severity in terms of increased percentage of BOP and mean percentage of sites with probing depths $\geqslant 5$ mm were found to be associated with inadequate glycaemic control as measured by HbA1c ($p < 0.01$). HsCRP was also found to be a significant predictor for mean percentage of sites with probing depths $\geqslant 5$ mm ($p < 0.05$). After controlling for age, gender, smoking habits and number of teeth, positive correlations were found between HbA1c and percentage sites with probing depths $\geqslant 5$ mm, percentage sites BOP, total cholesterol, LDL chol and triglycerides ($p < 0.05$). Using the adjusted differences, subjects with acceptable glycaemic control (HbA1c $< 8\%$) showed a lower percentage of sites with BOP and probing depths $\geqslant 5$ mm ($p < 0.05$) when compared with those having inadequate glycaemic control. There was also a trend towards lower blood cholesterol in the well-controlled group.

Conclusion: The level of glycaemic control as measured by HbA1c emerged as the most consistent risk factor associated with the extent and severity of periodontal disease in this study cohort.

Key words: diabetes; glycaemic control; HsCRP; lipid profile; periodontitis

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Conflict of interest and source of funding statement

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Dental biofilm is widely accepted as the main aetiological factor in periodontal disease. It is also clear that not all patients have similar susceptibility to periodontal disease in response to plaque (Socransky et al. 1998). Local and systemic factors have been implicated in the modulation of the host's inflammatory response (Page 1998). Of the systemic risk factors, it has been well established that patients with diabetes have at least a twofold increase in the severity of periodontal disease as compared with non-diabetics (Tervonen & Knuuttila 1986, Taylor 1999, Soskolne & Klinger 2001). Diabetes is also associated with other systemic complications, including increased risk for

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cardiovascular complications. In the management of diabetes, maintaining good glycaemic and lipid control are therapeutic objectives to reduce cardiovascular risk. To monitor metabolic control in diabetes, laboratory markers have been used to identify some of the systemic-related factors, which include lipid levels and to a lesser extent high-sensitivity C reactive protein (hsCRP). Elevations in blood glucose, hsCRP and cholesterol have also been found to be associated with periodontal disease severity (Loesche et al. 2000, Noack et al. 2001, Craig et al. 2003, D'Auito et al. 2004a, b).

HsCRP is currently one of the inflammation markers commonly used to identify cardiovascular risk (Pearson et al. 2003). While it is generally accepted that diabetic patients with poor glycaemic control have more severe periodontal disease, very few studies have investigated the influence of hsCRP and hyperlipidaemia on periodontal disease severity in diabetes.

This study aims to investigate the impact of common laboratory markers of metabolic control and inflammation in diabetes that may be associated with the extent and severity of periodontal disease.

Material and Methods

In the recruitment of subjects for the study, patients attending medical treatment at two diabetes centres from the period 2004 to 2005 were invited to participate in the study based on a set of inclusion criteria. The centres were chosen as they are two of the major diabetes referral centres in the country. The physicians and periodontists involved in the study also work in the same hospital premises, which facilitated the collaboration for the study.

The study sample comprises 181 adult patients aged 21–65 years (102 males and 79 females). The inclusion criteria for selection were subjects with type 1 or type 2 diabetes with at least eight natural teeth and having no known major medical complications such as coronary heart disease. Ethics approval was obtained before implementation of the study. Written informed consent was obtained from all patients. The evaluation consisted of a full-mouth periodontal assessment and analysis of blood for markers of metabolic control and inflammation. Patients' smoking habits were also recorded.

The periodontal parameters used to assess the periodontal health status of the participants were the presence of bleeding on probing (BOP) and probing depth measurement to the nearest millimetre. All assessments were carried out with the UNC 15 probe with 1 mm graduations; six sites around all teeth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual and disto-lingual) were examined. Periodontal assessment was carried out by two periodontists; intra- and inter-examiner calibrations were carried out before the study. The intra-examiner reproducibility ranged from 80% to 88% for BOP and probing; an inter-examiner reproducibility of 80–82% was obtained.

Blood samples were collected and analysed for glycated haemoglobin (HbA1c), hsCRP and lipid profile. HbA1c is a routine procedure used in most medical centres to monitor the glycaemic control of patients with diabetes. HsCRP is an acute-phase reactant used as a marker of systemic inflammation and as a cardiovascular risk marker. Assessment of lipid profile consisting of total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL chol) and high-density lipoprotein cholesterol (HDL chol) was also carried out. To ensure consistency, all the blood samples were sent to a single laboratory for analysis. The HbA1c values were determined using ion-exchange high-performance liquid chromatography. HsCRP was carried out in the Beckman Coulter's ''Immage'' immunochemistry system based on turbidimetric nephelometry with the lowest detection limit of 0.20 mg/l. Blood cholesterol and triglycerides were analysed by enzymatic methods. HDL chol was measured after precipitation with dextran sulphate and magnesium chloride. LDL chol was calculated using Friedewald's formula.

All data were entered into microcomputers; statistical analyses were carried out using the SPSS PC+14.00 software. To find out the potential biomarkers that are associated with periodontal disease severity, multiple regression models were carried out using %BOP, percentage of sites with probing depths $\geqslant$5 mm as dependent variables. The independent predictors were HbA1c, HsCRP, triglycerides, LDL, HDL, age group (1 – <45, 2 – $\geqslant$45), number of teeth, smoking (0 – Nil, 1 – Yes) and gender (1 – males, 2 – females). Collinearity diagnostics, Durban Watson tests and plot of residuals were also carried out to check the stability of the models. Pearson's partial correlation analyses were also performed to estimate the correlation of the various parameters. To compare the clinical and laboratory parameters for those with acceptable and unacceptable glycaemic control, student's *t*-tests were carried out for the unadjusted data; the adjusted differences and adjusted *p* levels were obtained from a series of linear regression analysis using glycaemic control as the dependent variable.

Results

Table 1 shows the mean percentage of sites with probing depths of various range categories, mean %BOP and levels of HbA1c, hsCRP and lipid profile by age and gender. Probing depths were categorized into three categories: $\leqslant$3, 4–5 and $\geqslant$6 mm. Over 80% of sites had probing depths $\leqslant$3 mm, 10% displayed probing of 4–5 mm and only a small proportion had probing depths $\geqslant$6 mm. The mean %BOP was 57.09. No significant difference was found between the two age categories and between genders. Total cholesterol, hsCRP and HbA1c were also comparable between the two age groups. (Table 1). Apart from slightly higher HDL chol levels found in females, no other differences were found between genders. Fifty-six per cent of the subjects presented with at least one site with probing depths 5 mm and above.

To investigate the relationship of surrogate markers with periodontal disease parameters (BOP, probing $\geqslant$5 mm), multiple regression analyses were performed. The independent variables were HbA1c, hsCRP, LDL chol, triglycerides, HDL chol, smoking, number of teeth, age and gender. When the %BOP was used as the dependent variable, HbA1c emerged as the single significant predictor variable ($p<0.05$). With percentage probing $\geqslant$5 mm as the dependent variable, HbA1c and hsCRP emerged as significant predictor variables ($p<0.05$) (Table 2). Collinearity diagnostics were also checked for the models. Tolerance levels of above 0.7 were achieved in all instances.

To explore the correlation between various blood and periodontal parameters, Pearson's correlation analyses were carried out after controlling for age, gender, number of teeth and smoking habits. There was a highly significant correlation between mean %BOP

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Table 1. Periodontal and laboratory parameters by age and gender

Parameter	Age <45		Age (⩾45)		Mean
	male ($N=38$)	female ($N=33$)	male ($N=64$)	female ($n=46$)	
%Probing ⩽3 mm	85.18 (20.5)	92.23 (8.6)	87.35 (17.8)	88.19 (20.3)	87.99 (17.8)
%Probing 4–5 mm	13.40 (18.2)	7.52 (8.2)	10.83 (14.5)	7.82 (12.9)	10.50 (14.7)
%Probing ⩾6 mm	1.42 (3.2)	0.26 (0.7)	1.82 (4.6)	2.02 (5.6)	1.50 (4.2)
%BOP	53.36 (23.8)	58.85 (22.91)	56.47 (25.51)	59.46 (24.54)	57.09 (24.40)
HbA1c %	7.59 (1.63)	8.04 (1.63)	7.89 (1.50)	8.10 (1.67)	7.93 (1.59)
HsCRP mg/l	2.24 (1.83)	3.79 (4.99)	2.13 (2.71)	3.35 (5.67)	2.79 (4.08)
Total cholesterol (mmol/l)	4.98 (1.00)	5.21 (1.04)	5.13 (1.05)	5.08 (0.91)	5.09 (0.90)
Triglycerides (mmol/l)	1.75 (1.04)	1.68 (2.09)	1.67 (0.90)	1.75 (0.86)	1.71 (1.23)
LDL mmol/l	3.00 (0.89)	3.19 (0.75)	3.21 (0.81)	2.95 (0.86)	3.09 (0.83)
HDL mmol/l	1.17 (0.45)	1.33 (0.38)*	1.18 (0.28)	1.38 (0.56)*	1.26 (0.43)
No. of teeth	27.66 (3.69)**	27.94 (3.53)**	21.92 (6.71)**	22.56 (6.17)**	24.38 (6.16)
%persons with probing ⩾5 mm	50.0	48.5	64.1	56.5	56.4

Standard deviation in parentheses.
*$p<0.05$ (males *versus* females).
**$p<0.05$ (age <45 *versus* age ⩾45).
HbA1c, glycated haemoglobin; HsCRP, high-sensitivity C Reactive Protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Multiple regression model with dependent variable: %BOP. %sites with probing ⩾5 mm

	%BOP				% Sites probing ⩾5 mm			
	unstandardized coefficient	SE	Significance	95% CI	unstandardized coefficient	SE	Significance	95% CI
HbA1c	3.62	1.21	0.003*	1.22–6.02	1.89	0.57	0.00**	0.75–3.02
HsCRP	0.20	0.50	0.67	−0.72–1.10	0.78	0.22	0.00**	0.35–1.21
Triglycerides	−0.30	1.98	0.88	−4.21–3.61	−1.39	0.94	0.14	−3.24–0.46
LDL	0.94	2.30	0.68	−3.61–5.48	−0.78	1.09	0.48	−2.92–1.38
HDL	−2.19	4.62	0.64	−11.32–6.94	−3.02	2.19	0.17	−7.34–1.31
Smoking (0 – nil, 1 – yes)	−3.78	6.34	0.60	−16.29–8.75	0.17	3.00	0.96	−5.76–6.10
Number of teeth present	−0.36	0.34	0.30	−1.01–0.32	0.24	0.16	0.14	−0.08–0.57
Age group (1 – <45, 2 – ⩾45)	1.39	4.2	0.74	−9.69–6.91	2.55	1.99	0.20	−1.38–6.48
Gender	2.60	3.94	0.51	−5.18–10.37	−3.31	1.87	0.08	−6.99–0.37
Constant	34.19	19.19	0.07	−3.72–72.01	−8.41	9.09	0.36	−26.37–9.55

*$p<0.05$,
**$p<0.01$.
HbA1c, glycated haemoglobin; HsCRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein, BOP, bleeding on probing.

and mean percentage of sites with probing depths ⩾5 mm ($p<0.001$). A positive correlation was also found between these periodontal parameters and HbA1c. For markers of metabolic control, HbA1c has a positive correlation with LDL chol, triglycerides and total cholesterol. (Table 3)

Table 4 compares the mean percentage of sites with probing depths of ⩽3, 4–5 and ⩾6 mm, %BOP, hsCRP and lipid profile of subjects with adequate and suboptimal glycaemic control. A cut-off level of 8% HbA1c was used to indicate the level of acceptable and unacceptable glycaemic control. Using the adjusted data, those with inadequate glycaemic control (⩾8%) were shown to have higher percentage bleeding, and higher mean percentage of sites with probing 4–5 and ⩾6 mm, but displayed lower percentage sites with shallow probing of ⩽3 mm. (Student's *t*-test $p<0.01$). Total blood cholesterol, LDL chol and triglycerides were also raised ($p<0.05$) in those with poorer glycaemic control.

Discussion

The findings of this investigation demonstrated a significant relationship between glycaemic control and periodontal health in terms of increased probing depths and BOP. There is also some indication that hsCRP is associated with periodontal disease progression in terms of increased probing depths.

The positive correlation between glycaemic control and severity of periodontal disease concurred with the findings from other reported studies (Bridges et al. 1996, Taylor et al. 1996). The reasons for poorer periodontal health among patients with poor glycaemic control could be explained by the hyperglycaemic state resulting in accumulation of advanced glycated end products. These products in turn lead to a cascade of inflammatory reactions leading to the release of inflammatory mediators like IL-1, IL-6, tumour necrosis factor α and CRPs, thereby enhancing the periodontal breakdown process (Lalla et al. 1998, Iacopino 2001, Bretz et al. 2005, Takeda et al. 2006). Tumour Necrosis factor α is known to induce insulin resistance, thus suggesting a possible bi-directional relationship between periodontal disease and diabetes. There is currently no consistent agreement as to whether periodontal treatment itself would result in improved glycaemic control (Aldridge et al. 1995, Christgau et al. 1998, Kiran et al. 2005). Nevertheless, achieving good glycaemic control appears to be a realistic approach

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Table 3. Pearson's correlations of the different parameters (controlled for age, gender, smoking and number of teeth)

	BOP	Probing ⩾5 mm	HbA1c	HsCRP	Triglyceride	LDL	HDL	Total Cholesterol
BOP		0.47**	0.25**	0.07	0.04	0.07	−0.06	0.06
Probing ⩾5 mm	0.47**		0.26**	0.30**	−0.03	0.00	−0.08	−0.07
HbA1c	0.25**	0.26*		0.13	0.16*	0.17*	−0.07	0.17*
HsCRP	0.07	0.30**	0.13		0.07	0.01	−0.10	−0.01
Triglyceride	0.04	−0.03	0.16*	0.07		0.06	−0.31**	0.32**
LDL	0.07	0.00	0.17*	0.01	0.06		−0.08	0.87**
HDL	−0.08	−0.13	−0.07	−0.10	−0.31**	−0.08		0.24**
Total cholesterol	0.06	−0.07	0.17*	−0.01	0.32**	0.87**	0.24**	

*$p<0.05$,
**$p<0.01$.
HbA1c, glycated haemoglobin; HsCRP, high-sensitivity C Reactive Protein; LDL, low-density lipoprotein; HDL, high-density lipoprotein, BOP, bleeding on probing.

Table 4. Comparison of mean %probing ⩽3, 4–5, ⩾6mm; % BOP, HsCRP and cholesterol of subjects with adequate and unacceptable glycaemic control with adjusted and unadjusted differences

Parameter	HbA1c <8% ($N=105$)	HbA1c ⩾8% ($N=76$)	Unadjusted		Adjusted	
			diff	*p* value	diff	*p* value
Probing ⩽3 mm	91.12 (15.00)	83.36 (20.58)	−6.76	0.007**	−8.93	0.001**
Probing 4–5 mm	7.98 (12.82)	14.23 (16.66)	6.25	0.008**	7.30	0.001**
Probing ⩾6 mm	0.89 (3.44)	2.41 (5.08)	1.51	0.03*	1.66	0.011**
BOP	52.29 (23.9)	63.74 (23.6)	11.45	002**	10.37	0.005**
HsCRP (mg/l)	2.48 (3.6)	3.00 (4.50)	0.52	0.32	0.39	0.53
Total Cholesterol (mmol/l)	4.94 (0.9)	5.31 (1.1)	0.37	0.01**	0.42	0.005**
Triglycerides (mmol/l)	1.53 (0.88)	1.95 (1.55)	0.42	0.04*	0.45	0.018*
LDL chol (mmol/l)	2.95 (0.79)	3.28 (0.84)	0.37	0.009**	0.35	0.007**
HDL chol (mmol/l)	1.31 (0.47)	1.21 (0.36)	−0.10	0.11	−0.11	0.10

Standard deviation in parentheses.
Diff, Difference (HbA1c ⩾8% from HbA1c <8%).
*$p<0.05$.
**$p<0.01$.
HbA1c, glycated haemoglobin; HsCRP, high-sensitivity C Reactive Protein; LDL chol, low-density lipoprotein cholesterol; HDL chol, high-density lipoprotein cholesterol.

to improve systemic health as well as periodontal health in diabetes. Research is needed in this area particularly in the local context as diabetes affects about 8–9% of the adult population (Ministry of Health 1999, 2004).

HsCRP has been identified as a risk marker for cardiovascular disease. In recent years, a positive correlation was also found between CRP and periodontal disease severity (Slade et al. 2000, Saito et al. 2003, D'Aiuto et al. 2004a, b, Loos 2005). There are several possible explanations for a significant association between CRP and increased probing depths for subjects in the present study. The presence of periodontal pathogens such as bacteriodes has been shown to stimulate an inflammatory response and release of cytokines by monocytes/macrophages and endothelial cells. IL-6 has been shown to induce CRP production; CRP, being an acute-phase reactant, has many pro-inflammatory effects. This may involve the potentiation of cytokines, activation of cell adhesion molecules in endothelial cells and complement activation (Craig et al. 2003, Joshipura et al. 2004). Although patients with elevated hsCRP appear to have more severe periodontal disease, the impact on BOP was less pronounced as gingival inflammation can be controlled if an individual practices effective plaque control. Participants in this study were patients attending treatment at specialist centres; presumably, they may be more co-operative and adherent in following medical advice including glycaemic and diet control. Furthermore, patients with known cardiovascular problems as verified from available medical records were excluded from the study at the outset. The majority of subjects presented with hsCRP <6 mg/l, a level well below the threshold value that would indicate cardiovascular risk. HsCRP was used as it was found to be more precise in measuring even small quantities of CRPs. The majority of the studies on CRP reported earlier in periodontal patients were carried out using the standard CRP and in non-diabetic patients. It has been found that the level of CRP is increased in hypertension and diabetes; it can also be influenced by smoking, diet and body mass index (King et al. 2003, Raitakari et al. 2005). On the other hand, CRP levels have been found to be lowered by the intake of statins (Ridker et al. 2005), a medication commonly prescribed to control hyperlipidaemia. In the current investigation, while a definite conclusion could not be drawn in relation to the effects of CRP on the severity of gingival inflammation in diabetes, there is some indication that hsCRP could be a potential risk marker in periodontal destruction

Hyperlipidaemia has been shown in a number of studies to be associated with periodontal breakdown in view of its pro-inflammatory reactions (Cutler et al. 1999, Katz et al. 2002, Morita et al.

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2004). The present investigation showed minimal impact on the severity of gingival inflammation. A possible explanation could be that a large proportion of subjects in the current study were given statins to control hyperlipidaemia as part of the therapeutic regimen, which therefore limits the results obtained. Nevertheless, subjects with unacceptable glycaemic control (HbA1c $\geqslant 8\%$) were found to have higher LDL chol and triglyceride levels than subjects with a more acceptable level of control. In the correlation analyses, triglycerides and LDL chol levels were also found to be correlated to glycaemic control. The association of elevated cholesterol with periodontal inflammation could be explained by the local production of cytokines and endotoxins from bacteria leading to changes in lipid metabolism (increased LDL chol, reduced HDL chol). The influence of HDL chol was, however, less marked in the present investigation as the majority of the sample has fairly good HDL chol levels. About 80% of the cohort had an acceptable HDL chol level of above 1 mmol/l.

Smoking has been documented as a risk factor in destructive periodontal disease (Tonetti 1998, Bergstrom et al. 2000). Contrary to findings from other studies (Syrjala et al. 2003, Jansson et al. 2006), in this study cohort, smoking did not appear to have a significant impact on the periodontal status. This could be explained by the low proportion of smokers as $<10\%$ of the participants were smokers. Smoking cessation is often incorporated into the overall management of diabetes; some patients might have quit smoking. Furthermore, as smokers are at a higher risk of cardiovascular problems, it is likely that some smokers might have been excluded from the sample at the outset. No conclusion on the effects of smoking could therefore be drawn from the study.

The findings in this study highlight a need to promote oral health in patients with diabetes as an integral component of total patient care. Longitudinal studies are needed to evaluate the long-term treatment outcome in terms of oral health as well as the systemic implications. Further studies with larger sample sizes are needed to investigate the cumulative influence of glycaemic control, lipid control and hsCRP in newly diagnosed patients with diabetes. In a multi-racial community in the local context, it would also be relevant to investigate the influence of ethnicity on the various serum markers and on periodontal disease.

The findings of this study confirm that poor glycaemic control is the most significant risk factor associated with periodontal health in terms of increased probing depths and more severe gingival inflammation in people with diabetes.

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Clinical Relevance

Scientific rationale for the study: With the emerging interest in the inter-relationship between periodontal disease and systemic factors, this study provides a practical approach in understanding diabetes as a risk factor in periodontal disease by utilizing surrogate markers commonly used in monitoring metabolic control of patients with diabetes. *Principal findings*: Based upon the current findings, the level of glycaemic control is the most significant risk factor associated with periodontal disease severity in diabetes. HsCRP, a cardiovascular risk marker, also appears to be linked with periodontal disease severity. *Practical implications*: The results highlight a need to monitor the impact of systemic risk factors on periodontal health. More controlled interventional studies are required to investigate possible causal relationships between metabolic control and periodontal health.

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