Journal of Clinical Periodontology
Official Journal of The European Federation of Periodontology
Founded by the British, Dutch, French, German, Scandinavian, and Swiss Societies of Periodontology

J Clin Periodontol 2009; 36: 11–17 doi: 10.1111/j.1600-051X.2008.01344.x

Journal of Clinical Periodontology

IL-6 $^{-174}$ genotype associated with the extent of periodontal disease in type 1 diabetic subjects

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Raunio T, Knuuttila M, Hiltunen L, Karttunen R, Vainio O, Tervonen T. IL-6 $^{-174}$ genotype associated with the extent of periodontal disease in type 1 diabetic subjects. J Clin Periodontol 2009; 36: 11–17. doi: 10.1111/j.1600-051X.2008.01344.x.

Abstract

Aim: The aim of this study was to investigate whether genetic polymorphism in certain cytokine and receptor molecule genes and diabetic status associate with the extent of periodontal disease in type 1 diabetes mellitus (DM).

Material and Methods: Eighty patients with type 1 DM participated. Visible plaque, bleeding on probing (BOP), probing pocket depth (PD) and attachment level (AL) were examined clinically and glycosylated haemoglobin (HbA1c) levels were used to assess the glycemic control of DM. CD-14, IL-6, TNF-α, IL-10, IL-1α, IL-1β and TLR-4 gene polymorphisms were studied using the polymerase chain reaction (PCR).

Results: The 3-year HbA1c was good (<7.5%) in 16%, acceptable (7.5–8.5%) in 36% and poor (>8.5%) in 48% of the subjects. IL-6 $^{-174}$ genotype and 3-year GHbA1c associated significantly with BOP and PD ⩾4 mm, subjects with the GG genotype of the IL-6 $^{-174}$ exhibiting more severe periodontal disease than those with the GC/CC genotype. After stratification by IL-6 genotype, associations between the extent of periodontal disease and 3-year HbA1c levels remained significant in subjects carrying the GC/CC but not the GG genotype.

Conclusions: In addition to the HbA1c level, the IL-6 $^{-174}$ genotype is a significant susceptibility factor for periodontal disease among type 1 diabetics.

Key words: gene polymorphism; glycemic control; IL-6; periodontal disease; type 1 diabetes mellitus

Accepted for publication 28 September 2008

Diabetes mellitus (DM) increases the risk of periodontal disease (Taylor 2001, Mealey & Oates 2006). Based on previous studies, the level of glycemic control (Tervonen & Oliver 1993, Lalla et al. 2007, Lim et al. 2007), the presence of diabetic complications (Karjalainen & Knuuttila 1996, Shultis et al. 2007) and disease duration (Firatli et al. 1996, Tervonen et al. 2000) are important determinants of this relationship. Pathogenetic mechanisms behind the increased severity of periodontal disease among diabetic subjects include impaired function of immune cells (American Academy of Periodontology 1999), alterations in collagen metabolism (Gooch et al. 2000, Lu et al. 2003) and inflammatory response to oral pathogens (Naguib et al. 2004, Graves et al. 2005), and an increased rate of apoptosis of the matrix-producing cells in a hyperglycemic state (Liu et al. 2004, Graves et al. 2007).

The exaggerated immunoinflammatory response of the host may be one reason for the increased prevalence and severity of periodontal disease seen in diabetic patients (Graves et al. 2005, Mealey & Oates 2006). The hyperglycemic state results in accumulation of advanced glycated end products (AGES). This in turn leads to the release of inflammatory mediators such as cytokines IL-1, IL-6, TNF-α and C- reactive protein (CRP) thereby enhancing the periodontal breakdown process (Grossi 2001, Iacopino 2001, Takeda et al. 2006, Lim et al. 2007).

Genetically transmitted traits such as gene polymorphisms may accentuate the host's inflammatory response to a bacterial challenge and account for variation in individual susceptibility to periodontitis (Michalowicz et al. 2000, Yoshie et al. 2007). Although periodontitis is a multi-factorial disease and microbial and environmental factors initiate and modify disease progression, findings from several studies suggest that the severity and progression of periodontal disease might be associated with cytokine gene polymorphisms (Takashiba & Naruishi 2006, Yoshie et al. 2007). However, the results of the studies are somewhat controversial, and

Conflict of Interest and Source of Funding Statement

The authors declare that they have no conflict of interests.
The financial help by The Finnish Dental Society Apollonia is highly appreciated.

until now, no specific genetic risk factor of periodontitis has been identified (Loos et al. 2005, Huynh-Ba et al. 2007). Genetic variants of cytokine IL-1 (Kornman et al. 1997, Laine et al. 2001), TNF-α (Soga et al. 2003, Donati et al. 2005) and IL-6 (Trevilatto et al. 2003, D'Aiuto et al. 2004) genes have been suggested to be involved in the pathogenesis of periodontitis. We have recently shown that $CD14^{-260}$ and $IL\text{-}6^{-174}$ are associated with the extent of periodontal disease in non-diabetic subjects with moderate to severe periodontitis after controlling for significant confounding factors (Tervonen et al. 2007).

There is heterogeneity in the incidence and severity of periodontal disease in the diabetic population (Mealey & Oates 2006, Lalla 2007). Besides risk factors such as glycemic control, there may be mechanisms so far unknown that contribute to the initiation and progression of periodontal disease in diabetic subjects. We examined the periodontal health and diabetes status of a group of type 1 diabetic subjects. We also studied polymorphisms in the genes that encode the following cytokines and inflammatory molecules: CD14, IL-6, TNF-α, IL-10, IL-1α, IL-1β and TLR-4. In the present study, our aim was to investigate the significance of the above factors in relation to the expression of periodontal disease in type 1 diabetic subjects.

Material and Methods

Subjects

A total of 80 patients (46 females and 34 males) mainly recruited from primary health care diabetes unit with type 1 DM and of Caucasian origin volunteered to participate (Table 1). A few patients were recruited from the Clinic of Internal Medicine of Oulu University Hospital. The mean age (± SD) of the subjects was 38.9 years (± 12.3) (range 19–74 years). The informed consent of the subjects was obtained and the study protocol was accepted by the Ethical Committee of the Faculty of Medicine, University of Oulu, Finland. Subjects needing prophylactic antibiotic medication in association with periodontal probing as well as those with immunosuppressive medication or antibiotics during the past 4 months were excluded from the study. The reference group ($n = 178$) representing normal population consisted of university staff and students of Caucasian origin (122 females and 56 males aged 39.4 ± 13.4 years) who were informed of the study and volunteered to give their blood samples to be used as reference samples (Karhukorpi et al. 2002). The genotype frequencies of the two groups were compared, and no data concerning general health or periodontal status of the subjects of the reference group was collected.

Diabetes status

Glycosylated haemoglobin values (HbA1c) were tested from the diabetic patients at the time of the clinical examination. Based on patient records, the mean value of the HbA1c levels over the past 3 years (3-year HbA1c) was calculated to indicate the long-term control of DM (on the average 6.6 measurements/subject). While a laboratory immunoassay method was used to analyse the HbA1c level at the time of the clinical examination, the 3-year values were based both on a laboratory immunoassay and on measurements using a DCA device in the diabetes clinic. Diabetic complications were registered from the patient records and categorized as follows: the presence or absence of retinopathy (proliferative or non-proliferative stage), nephropathy (micro- or macroalbuminurea), peripheral neuropathy and macrovascular complications (stroke or myocardial infarction). Data concerning smoking habits were obtained by interviewing the subjects in association with the clinical examination and the subjects were categorized as non-smokers and smokers. There were altogether 56 non-smokers who ever smoked. The group of smokers comprised 15 smokers who smoked either occasionally or <10 cigarettes per day and of nine subjects smoking $\geqslant 10$ cigarettes per day.

Table 1. Subject characteristics: means ± standard deviations or numbers of subjects

Parameter	
Age, years (range)	38.9 ± 12.3 (19–74)
Gender (n)	
Females/males	46/34
Diabetes parameters	
Duration of diabetes, years (range)	19.9 ± 11.9 (1.2–48.1)
Current HbA1c,* % (range)	8.5 ± 1.4 (5.6–12.9)
3-year HbA1c,† % (range)	8.5 ± 0.1 (5.6–12.2)
<7.5/7.5–8.5/>8.5	13/29/38
Presence/absence	
Retinopathy	46/34
Nephropathy	19/61
Peripheral neuropathy	7/63
Stroke or myocardial infarction	6/74
Smoking habits	
Non-smoker/smoker	56/24
Periodontal parameters (mean % of sites ± SD)	
Dental plaque	31.3 ± 23.6
Bleeding on probing	68.2 ± 16.5
PD ⩾ 4 mm	24.2 ± 20.3
AL ⩾ 4 mm	13.8 ± 24.0

*HbA1c at the time of the examination.
†Mean value of HbA1c over the past 3 years.
PD, pocket depth; AL, attachment level.

Clinical periodontal examination

The clinical periodontal examination of all the subjects was performed by the same periodontal specialist (T. R.) at the Special Oral Health Care Unit of City of Oulu. Periodontal variables were recorded at four sites (mesiobuccal, midbuccal, distobuccal and midlingual) of all teeth excluding third molars. The presence of visible plaque was assessed after gentle drying with air corresponding to the criteria of scores 2 and 3 of the plaque index (Silness & Löe 1964). Probing pocket depth (PD) was measured using a ball-pointed periodontal probe with 2 mm graduations from the gingival margin to the base of the crevice/pocket. Bleeding on probing (BOP) was scored positive if a site bled within 20–30 s after probing. Periodontal attachment level (AL) was measured from the cemento-enamel junction to the base of the crevice/pocket.

Cytokine gene polymorphism

Patient's DNA was extracted from an EDTA blood sample, and CD14^{-260}, IL-6^{-174}, TNF-α^{-308}, IL-10^{-1082}, IL-1α^{-889}, IL-1β^{+3954} and TLR4^{+896} genotypes were tested using polymerase chain reaction (PCR). The genotypes in each cytokine gene were grouped according to their known biological significance, as detailed previously (Tervonen et al. 2007). Accordingly, a genotype/genotypes known to produce higher levels of the cytokine (positive genotype) were estimated separately from the one(s) known to be associated with lower secretion. As regards the genotype frequencies, deviations from Hardy–Weinberg equilibrium were assessed using Pearson's goodness of fit method between the observed and expected frequencies in the control group.

Data analysis

The extent of sites with plaque, BOP, PD$\geqslant$4 mm and AL$\geqslant$4 mm were calculated as percentages of affected sites out of the total number of sites measured. Subject characteristics were expressed as means ($\pm$ SD) and distributions of subjects (Tables 1 and 2). The frequencies of the cytokine genotypes (Table 2) and allele frequencies of the single nucleotide polymorphisms (SNPs) between the diabetic and the reference subjects were compared using the χ^2-test. Both unadjusted and adjusted associations between the extent of BOP and PD$\geqslant$4 mm, and their determinants were calculated using linear regression analysis (Tables 3 and 4). Because of several risk factors and multiple comparisons, we considered p-values <0.01 as statistically significant.

Results

The subjects of the present study had suffered from type 1 diabetes on average 19.9 years (range 1.2–48.1 years). Retinopathy (57.5%) and peripheral nephropathy (23.7%) were the most common diabetic complications. For the whole group, the mean HbA1c level ($\pm$ SD) at the time of the clinical examination was 8.5% ($\pm$ 1.4) and the 3-year HbA1c 8.5% ($\pm$ 0.4). The mean range per patient, i.e. the mean difference between the lowest and the highest HbA1c value, was on average 2.0%. When further evaluating the 3-year HbA1c, the patients were classified into three subgroups: good $<$7.5% (16.3%), acceptable 7.5–8.5% (36.3%) and poor $>$8.5% (47.5%).

As regards the periodontal health status, one-third of the sites (31.3%) harboured plaque and over two-thirds were BOP (68.2%). The extent of PD$\geqslant$4 mm was 24.2% and 13.8% of the sites presented AL$\geqslant$4 mm (Table 1).

No statistically significant differences were found in the frequencies of the cytokine genotypes between the diabetic patients and the reference subjects when any of the SNPs was considered (Table 2). Also the allele frequencies of the SNPs were similar in the two subject groups ($p>0.01$, data not shown). The Hardy–Weinberg equilibrium criteria were fulfilled in the reference group for all the other genotypes except for IL-1α^{-889}. The reason for its genotype frequency deviation is not known but does not, however, affect our results as the genotype frequencies of IL-1α^{-889} were the same in the diabetes and reference groups.

The unadjusted associations between the extent of BOP and PD$\geqslant$4 mm are shown in Table 3. The 3-year HbA1c was significantly associated with the extent of BOP ($p=0.001$). The duration of the disease and 3-year HbA1c were also significantly associated with the extent of PD$\geqslant$4 mm ($p=0.004$, 0.002, respectively). Of all cytokine genotypes examined, only the IL-6^{-174} genotype turned out to be significantly associated with the extent of both BOP and PD$\geqslant$4 mm. When compared with the subjects with the CC/CG genotype of IL-6^{-174}, those carrying the GG genotype had significantly more sites with BOP (79% *versus* 65%) and PD$\geqslant$4 mm (38% *versus* 20%) (Fig. 1). The 3-year HbA1c ($\pm$ SD) was slightly higher in subjects carrying the GG than the GC/CC genotype (8.8% *versus* 8.4%).

The associations between the extent of BOP and PD$\geqslant$4 mm, and the IL-6^{-174} genotype and the 3-year HbA1c were further studied using a regression model (Table 4). Adjustments were made for plaque, age, duration of diabetes, smoking and gender. The IL-6^{-174} genotype and 3-year HbA1c were statistically significantly associated with BOP ($p=0.009$, 0.007, respectively) and PD$\geqslant$4 mm ($p=0.009$, 0.009, respectively).

After stratification by IL-6^{-174} genotype, the associations between BOP and PD$\geqslant$4 mm, and 3-year HbA1c levels remained significant in subjects carrying the GC/CC but not the GG genotype (Table 5).

Table 2. Distribution of the genotypes in the type 1 diabetic subjects and reference subjects (the positive genotype is highlighted)

Genotype	Type 1 diabetes subjects *n* (%)	Reference subjects *n* (%)
CD 14^{-260}		
CT/TT	46 (57.5)	101 (56.7)
CC	34 (42.5)	77 (43.3)
IL-6^{-174}		
GG	17 (21.3)	37 (20.8)
CG/CC	63 (78.7)	141 (79.2)
TNF-α^{-308}		
GG	59 (73.8)	137 (77.0)
AG/AA	21 (26.3)	41 (23.0)
IL-10^{-1082}		
AA	29 (36.3)	54 (30.3)
AG/GG	51 (63.7)	124 (69.7)
IL-1α^{-889}		
CT/TT	44 (55.0)	76 (42.7)
CC	36 (45.0)	102 (57.3)
IL-1β^{+3954}		
CT/TT	28 (35.0)	78 (43.8)
CC	52 (65.0)	100 (56.2)
TLR4^{+896}		
AG/GG	15 (18.8)	36 (20.2)
AA	65 (81.3)	142 (79.8)

χ^2-test, $p>0.01$ for all comparisons between the diabetic and the control group.

Discussion

To date, only a few studies have been made to investigate whether gene polymorphisms of certain cytokine genes are

Table 3. Unadjusted associations between percentages of sites with gingival bleeding (BOP) and periodontal pocketing (PD⩾4 mm) and explanatory variables

	BOP			PD⩾4 mm		
	β	95% CI	*p*	*β*	95% CI	*p*
Age	0.41	0.12–0.70	0.006	0.56	0.21–0.91	0.002
Gender (male *versus* female)	0.55	−6.92–8.02		5.37	−3.76–14.50	0.057
Smoking (yes *versus* no)	4.71	−3.29–12.70		9.43	0.27–19.13	
Plaque	0.38	0.24–0.51	<0.001	0.48	0.32–0.64	<0.001
Duration of diabetes	0.36	0.04–0.65	0.028	0.55	0.18–0.92	0.004
Current HbA1c*	3.08	19.56–64.27	0.02	2.98	−29.22–26.61	
3-year HbA1c†	4.79	2.06–7.53	0.001	5.61	2.21–9.00	0.002
Complications‡						
Retinopathy	2.51	−4.94–9.97		0.63	−8.58–9.84	
Nephropathy	6.69	−1.86–15.24		2.43	−8.25–13.11	
Neuropathy	8.84	−4.08–21.77		6.30	−9.75–22.34	
Stroke and/or myocardial infarction	11.35	−2.44–25.14		8.25	−8.90–25.43	
Genotype§						
$CD14^{-260}$	1.60	−5.86–9.07		3.37	−5.80–12.55	
$IL\text{-}6^{-174}$	13.59	5.09–22.09	0.002	16.89	6.43–27.35	0.002
$TNF\text{-}\alpha^{-308}$	3.09	−5.28–11.46		5.40	−4.87–15.68	
$IL\text{-}10^{-1082}$	2.54	−5.13–10.20		0.73	−8.74–10.20	
$IL\text{-}1\alpha^{-889}$	2.69	−4.71–10.09		0.72	−9.87–8.43	
$IL\text{-}1\beta^{+3954}$	0.62	−7.13–8.37		1.03	−10.57–8.51	
$TLR4^{+896}$	4.28	−5.14–13.70		5.00	−6.61–16.61	

Continuous variables: age (years), percentages of sites with plaque, duration of diabetes mellitus (years).
*HbA1c at the time of the examination.
†Mean HbA1c value over the past 3 years.
‡Complications: subjects with complications compared with those without.
§Genotypes: $CD14^{-260}$ (CT/TT *versus* CC), $IL\text{-}6^{-174}$ (GG *versus* CG/CC), $TNF\text{-}\alpha^{-308}$ (GG *versus* AG/AA), $IL\text{-}10^{-1082}$ (AA *versus* AG/GG), $IL\text{-}1\alpha^{-889}$ (CT/TT *versus* CC), $IL\text{-}1\beta^{+3954}$ (CT/TT *versus* CC), $TLR4^{+896}$ (AG/GG *versus* AA).

Table 4. Plaque, age, duration of diabetes mellitus (DM), smoking and gender-adjusted associations between gingival bleeding (BOP) and periodontal pocketing (PD⩾4 mm) and 3-year HbA1c and $IL\text{-}6^{-174}$ genotype

	BOP (% sites)				PD⩾4 mm (% sites)			
	β	95% CI	*p*	R^2	*β*	95% CI	*p*	R^2
3-year HbA1c*	3.24	0.94–5.55	0.007		3.64	0.94–6.35	0.009	
$IL\text{-}6^{-174}$ genotype†	9.61	2.46–16.76	0.009		11.28	2.92–19.64	0.009	
Plaque	0.34	0.21–0.47	<0.001		0.39	0.24–0.54	<0.001	
Age	0.16	−0.11–0.44	0.237		0.18	−0.14–0.50	0.279	
Duration of DM	0.09	−0.20–0.37	0.546		0.28	−0.05–0.61	0.098	
Smoking‡	5.66	−0.38–11.70	0.066		11.17	4.02–18.24	0.002	
Gender§	4.32	−1.71–10.34	0.157	0.502	−0.08	−7.13–6.97	0.982	0.548

*Continuing variables: mean HbA1c value over the past 3 years, percentages of sites with plaque, age (years), duration of DM (years).
†IL-6 genotype: GG *versus* GC/CC.
‡Smoking: smokers *versus* non-smokers.
§Gender: males *versus* females.

associated with periodontal disease in diabetic patients. A recent cross-sectional study (Struch et al. 2008) reported an increase in the severity of periodontal disease along with increasing levels of HbA1c among type 2 diabetic subjects and further, there was a significant association between T-bearing risk genotype of IL-1A/1B and periodontal disease in diabetic but not in non-diabetic subjects. Another study (Guzman et al. 2003) also found a trend suggesting that allele 1 at IL-1B was over-represented among diabetic subjects with periodontal disease. On the other hand, in a study by Perez et al. (2004), TNF-α promoter polymorphism did not associate with the presence of aggressive periodontitis in subjects with type 1 DM.

To our knowledge, this is the first study reporting that the IL-6 gene polymorphism may have influence on the severity of periodontal disease in type 1 diabetic subjects. The main finding was that $IL\text{-}6^{-174}$ genotype was significantly associated with the extent of periodontal disease, those with the GG genotype exhibiting a significantly higher extent of BOP and PD⩾4 mm than those carrying the CG/CC genotype (Fig. 1, Table 4).

IL-6 is a pleiotropic cytokine with important roles in the regulation of the immune response, inflammation and haematopoiesis (Gabay 2006, Nishimoto & Kishimoto 2006). An association between IL-6 gene polymorphism at position −174 and periodontal disease has been found in many studies (Trevilatto et al. 2003, D'Aiuto et al. 2005, Brett et al. 2005, Tervonen et al. 2007), although

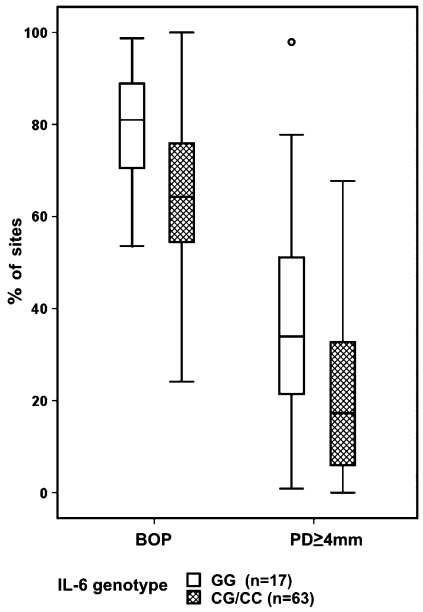

Fig. 1. Extent of bleeding on probing (BOP) and PD ⩾ 4 mm by IL-6 $^{-174}$ genotype. When compared with the subjects with the CG/CC genotype, those with the GG genotype had significantly more sites with BOP ($p = 0.002$) and PD ⩾ 4 mm ($p = 0.002$).

Table 5. Plaque-adjusted associations between bleeding on probing (BOP) and periodontal pocketing (PD ⩾ 4 mm) and 3-year HbA1c* separately in subjects with the GG and CG/CC IL-6 $^{-174}$ genotype

	BOP (% sites)			PD ⩾ 4 mm (% sites)		
	β	95% CI	*p*	*β*	95% CI	*p*
GG genotype						
3-year HbA1c	1.09	− 3.26–5.43	0.600	2.99	− 6.16–12.14	0.495
GC/CC genotype						
3-year HbA1c	4.31	1.62–6.99	0.002	4.54	1.74–7.34	0.002

*Mean HbA1c value over the past 3 years.

the reports are conflicting, which genotype (GG or GG/CG) is involved in the risk of periodontal damage. There seem to be other functional IL-6 polymorphic sites, at least − 572, − 1363, − 1480 and − 6106 (Terry et al. 2000, Fife et al. 2005, Nibali et al. 2008) and according to Nibali et al. (2008), the conflicting results might be explained by synergistic effects of the different SNPs and their function in linkage disequilibrium. Therefore, it is possible that IL-6 SNPs also in positions other than − 174 may be behind the increased extent of BOP and PD ⩾ 4 mm in the present subjects carrying the GG genotype (Fig. 1). However, the specific SNP at − 174 position and GG genotype of it seems to be a good marker for genetically determined hyperproduction of IL-6 in our Finnish population as shown in studies related not only to periodontitis (Raunio et al. 2007) but also to a systemic inflammatory disease as well (Hulkkonen et al. 2001).

In the present study, we also found that the glycemic control of the type 1 diabetes over the preceding 3 years was associated with the extent of periodontal disease (Table 4), which is in line with earlier studies (Tervonen & Karjalainen 1997, Mealey & Oates 2006, Lim et al. 2007). One mechanism, through which chronic hyperglycemia contributes to the severity of periodontal disease, is that it accelerates the formation of the so-called AGEs. AGEs in turn affect the secretion of cytokines and other inflammatory mediators through interacting by monocytic cell-surface receptors (RAGEs). Salvi et al. (1997a, b) reported that the secretion of TNF-α, IL-*β* and PGE2 after *Porphyromonas gingivalis* lipopolysaccharide (LPS) stimulation was higher by monocytes from insulin-depended diabetes mellitus (IDDM) patients than by monocytes from systemically healthy controls. The release of the inflammatory mediators showed large inter-individual variation, extremely high concentrations being secreted by some IDDM patients. The abnormal monocytic response to LPS was associated with the diabetic state, a hyperresponsive monocytic phenotype and, importantly, with more severe periodontal disease. In the context of the present study, one may hypothesize that hyperglycemia contributed to the monocytic release of IL-6 of the present type 1 diabetic subjects as well; the worse was the control of diabetes, the greater was the production of both local and systemic IL-6, and the worse was the periodontal health. The higher extent of periodontal disease in the GG genotype subjects (Fig. 1), on the other hand, can be seen as a result of the previously shown higher production of IL-6 by subjects carrying this special genotype (Fishman et al. 1998, Hulkkonen et al. 2001, Raunio et al. 2007). That a significant association between the extent of periodontal disease and the glycemic control could be found in subjects carrying the CC/CG but not the GG genotype (Table 5) may indicate that there were stronger factors, evidently the genotype itself, that overshadowed the influence of the glycemic control on periodontal disease in subjects carrying the GG genotype.

Type 1 diabetes is a chronic autoimmune disease associated with multiple genetic and environmental risk factors. The role of cytokine gene polymorphism, including IL-6 polymorphism, has also been investigated in order to determine possible contributions to type 1 diabetes susceptibility. Only marginal or inconsistent evidence has been published to support the role of the IL-6 $^{-174}$ (G > C) polymorphism in the pathogenesis of the type 1 diabetes. In a recent meta-analysis, however, the role of IL-6 gene could not be excluded (Cooper et al. 2007). In our study, the distributions of the subjects by the IL-6 $^{-174}$ genotype were similar between the diabetic and the reference subjects (Table 2), and thus no overrepresentation of either of the genotypes (GG and CG/CC) in the diabetic group could be observed.

The shortcomings of this study include that no statistical power calculation of sample size was performed.

However, we consider the strong associations between the extent of both BOP and PD $\geqslant$ 4 mm, and IL-6^{-174} genotype in the 80 subjects as indicative of the role of this genotype in periodontal diseases in type 1 DM. After stratifying the study population by genotype, the number of subjects in the GG group was fairly small. Therefore, the finding that the association between the extent of periodontal disease and the glycemic control is dependent on the IL-6^{-174} genotype should be interpreted with caution. Further, the use of two different methods in assessing the past HbA1c values may have caused some inaccuracy in the assessment of the mean HbA1c level over the 3 years before the study.

In conclusion, a new finding was that the IL-6^{-174} genotype was a significant determinant for the expression of periodontal disease among the present type 1 diabetic subjects. The association between the extent of periodontal disease and glycemic control was dependent on the IL-6^{-174} genotype. Possible interactions between the IL-6^{-174} genotype and the glycemic control in relation to periodontal disease should be studied using larger samples.

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Clinical Relevance

Scientific rationale for the study: Besides already known risk factors such as glycemic control, polymorphisms in the genes that encode proinflammatory cytokines may contribute to the expression of periodontal disease in diabetic subjects.

Principal findings: In addition to glycemic control, the IL-6^{-174} genotype associated significantly with the extent of periodontal disease; subjects with the GG genotype were more severely affected. The association between the extent of periodontal disease and glycemic control of DM was dependent on the IL-6^{-174} genotype.

Practical implications: The IL-6 genotype should be taken into account when evaluating the relationship between glycemic control and periodontal disease.