

Inverse association between periodontitis and respiratory allergies in patients with type 1 diabetes mellitus

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Friedrich N, Kocher T, Wallaschofski H, Schwahn C, Lüdemann J, Kerner W, Völzke H. Inverse association between periodontitis and respiratory allergies in patients with type 1 diabetes mellitus. *J Clin Periodontol* 2008; 35: 305–310. doi: 10.1111/j.1600-051X.2008.01200.x.

Abstract

Aim: In a general adult population, we have demonstrated an inverse association between periodontitis and respiratory allergies that is in line with the hygiene hypothesis suggesting a protective effect of infections against the development of allergies. The objective of the present study was to investigate the association between periodontitis and respiratory allergies in a type 1 diabetes mellitus population.

Material and Methods: The study population comprised 170 patients with type 1 diabetes mellitus aged 17–80 years. Respiratory allergies were present in 22 subjects. The attachment loss (AL) was measured. Periodontitis was defined according to the percentage of surfaces that exceeded 3 mm AL (healthy, mild, moderate, severe periodontal conditions).

Results: Our adjusted analyses revealed an inverse association between periodontitis and respiratory allergies. For increasing AL, a trend towards a decreasing risk was present for respiratory allergies ($p_{\text{trend}} < 0.05$). Compared with subjects with healthy periodontal conditions, individuals with severe periodontal conditions had the lowest risk of respiratory allergies [odds ratios (OR) 0.06 (95% confidence interval (CI) 0.01–0.39)], followed by subjects with moderate AL [OR 0.14 (95% CI 0.03–0.63)] and mild AL [OR 0.32 (95% CI 0.09–1.08)].

Conclusion: There is a strong inverse association between periodontitis and respiratory allergies in patients with type 1 diabetes mellitus. These findings further support the hygiene hypothesis.

Key words: allergies; diabetes mellitus type 1; periodontitis; study of health in Pomerania

Accepted for publication 8 December 2007

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests. The Study of Health in Pomerania (SHIP) is part of the Community Medicine Net (<http://www.medizin.uni-greifswald.de/cm>) of the University of Greifswald, which is funded by grants from the German Federal Ministry of Education and Research (BMBF, Grant 01ZZ96030); the Ministry for Education, Research, and Cultural Affairs; and the Ministry for Social Affairs of the Federal State of Mecklenburg – West Pomerania.

Recently, we demonstrated an inverse association between periodontitis and respiratory allergies in a general adult population (Friedrich et al. 2006). The risk of hayfever or house dust mite (HDM) allergy decreased with increasing attachment loss (AL). Our data supported the hygiene hypothesis (Strachan 1989) by suggesting a protective effect of infections against the development of allergies. A possible explanation for the hygiene hypothesis presents the T-helper type 1 (Th1)/Th2 paradigm (Mosmann & Coffman 1989, Romagnani 1992), which indicates that

Th2-derived cytokines inhibit the development of Th1 cells and vice versa. Against the background that allergic diseases are Th2-mediated, whereas Th1 cells predominantly trigger infections, the inverse association between periodontitis and respiratory allergies is well in accordance with the Th1/Th2 paradigm.

The aim of the present study is to investigate a possible inverse association between periodontitis and respiratory allergies in a population of patients with type 1 diabetes mellitus. A number of studies reported that patients with

type 1 diabetes mellitus had a higher risk of periodontal disease (Genco 1996, Kinane & Chestnutt 1997) and significantly more teeth affected by AL (Grossi et al. 1994, Firatli 1997, Lalla et al. 2006) than healthy subjects. On the other hand, previous studies have demonstrated that patients with type 1 diabetes mellitus had less common symptoms of asthma (Douek et al. 1999, Meerwaldt et al. 2002), hayfever, or eczema (Meerwaldt et al. 2002). Also, a meta-analysis (Cardwell et al. 2003) revealed a lower risk of asthma and eczema in patients with type 1 diabetes mellitus compared with healthy references. An inverse association between periodontitis and atopic allergies might thus link the positive association between type 1 diabetes mellitus and periodontal disease and the negative association between type 1 diabetes mellitus and respiratory diseases. Therefore, we hypothesize that if an inverse association between periodontitis and atopic allergies might be replicated in a homogeneous subgroup of patients with type 1 diabetes mellitus, the strength of such an inverse association would have been stronger in the latter compared with non-diabetic subjects randomly selected from the general population.

Material and Methods

Study population

Subjects were patients with type 1 diabetes mellitus aged 17–80 years who were recruited from the Center of Cardiology and Diabetes, Karlsburg and surrounding practicing diabetologists. Inclusion criteria were German citizenship and residency in West Pomerania, the northeasternmost part of Germany. Data collection was performed between December 1997 and December 2000. A total number of 233 patients with type 1 diabetes mellitus were examined. All participants gave informed written consent. The Ethics Committee of the University of Greifswald approved the study.

Of the 233 participants, 62 individuals who had no oral examination or who had fewer than 12 of 56 measuring points for the AL, and one participant who refused the interview were excluded from the analyses. Altogether, the final study population thus comprised 170 subjects who were available for the present analyses.

Measurements

The interview as well as the physical and oral health examinations of the patients with type 1 diabetes mellitus were performed using the standard protocol of the Study of Health in Pomerania (SHIP) by identical examiners as reported recently (Friedrich et al. 2006). Trained dentists assessed the dental status. Periodontitis was measured by cumulative AL, which represents the distance from the cemento-enamel junction to the bottom of the periodontal pocket. The measurements were performed on a maximum of 14 teeth on four surfaces: mesiobuccal, distobuccal, midbuccal, and midlingual and made in whole millimetres, either on the left or the right quadrant in alternate subjects. The severity and extent of periodontitis were determined by the mean of AL over all assessed teeth. Subjects were categorized into four groups according to the quartiles of distribution (healthy periodontal conditions: 0–1.1 mm, mild: 1.1–1.9 mm, moderate: 1.9–3.1 mm, and severe: > 3.1 mm AL). Furthermore, for each subject, the percentage of surfaces that exceeded 3 mm AL was determined. Regarding the last mentioned variable, subjects were also categorized into four groups according to the quartiles of distribution (healthy periodontal conditions: 0–7.6%, mild: 7.7–27.0%, moderate: 27.1–54.2%, and severe: > 54.2% AL > 3 mm). Coronal carious lesions, fillings, secondary caries, and missing teeth were registered by surface, with the exception of wisdom teeth. The decayed, missing, and filled surface (DMFS) index and decayed, missing, and filled tooth (DMFT) index were calculated according to World Health Organization (1997) criteria. Subjects were categorized into four groups according to the quartiles of distribution (DMFT: low, <6; mild, 6 and 7; moderate, 8–10; high, >10; DMFS: low, <12; mild, 12–23; moderate, 24–37; high, >37).

A computer-aided personal interview was used to collect information on the medical history, behavioural, and socio-demographic characteristics. Hayfever and HDM allergy were defined according to self-reported answers to the following two questions: (1) Do you have any allergies?; (2) Which allergies on the following list do you have? (Friedrich et al. 2006). Asthma was assessed by the three key questions: (1) Have you had wheezing or whistling

in the chest during the past 12 months?; (2) Have you had this wheezing or whistling when you did not have a cold?; (3) Do you take any anti-asthmatic medication at present, e.g. tablets, spray, or inhalations? Asthma was defined as a positive response to either questions (1) and (2), or to question (3) alone (Friedrich et al. 2006). Chronic bronchitis was defined as productive cough in the past 12 months for at least 3 months. Subjects with chronic bronchitis were classified as non-asthmatics. Respiratory allergies were present if subjects reported a positive history for either hayfever, HDM allergy, or asthma (Friedrich et al. 2006). A positive family history of allergies or asthma was present if one of the biological parents had one allergy or asthma. The school education level was categorized into two levels [low (≤ 10 years), high (> 10 years)]. As to smoking status, subjects were categorized into current, former, and never-smokers. Two categories for alcohol consumption were defined using the consumed amount of alcohol in grams per day [low (women: <20 g/day, men: <30 g/day) and high (women: ≥ 20 g/day, men: ≥ 30 g/day)]. Serum haemoglobin (Hb) A1C was determined as per high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany).

Statistical analysis

Continuous data are expressed as mean and standard error. Nominal data are expressed as percentage. For bivariate analyses, the χ^2 test (nominal data) or the Mann-Whitney *U*-test (continuous data) was used to compare subjects with and without respiratory allergies. Multivariable logistic regression models were run to assess the associations between periodontitis and respiratory allergies. As possible confounders, sex, age, school education, smoking, alcohol consumption, a family history of allergies or asthma, diabetes duration, and serum Hb A1c level were considered. The confounder selection was performed by a two-step procedure. The preliminary step to multivariable model development was to fit a one-predictor model for each possible confounder. Only diabetes duration had a *p*-value <0.25 and was included in the multivariable model. In addition, sex, age, and smoking were chosen because of their biological interest. In the second step, all variables with a *p*-value >0.10 were

excluded if the inclusion in the model did not lead to a $\geq 10\%$ change in the coefficient of interest. The final models were adjusted for sex, age, smoking, and diabetes duration. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. Further tests for trend in AL-related risk of allergies were performed by fitting this variable as a continuous covariate in the logistic regression model. A value of $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed with SAS version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Results

Overall, respiratory allergies were present in 12.9% ($n = 22$) of the investigated patients with type 1 diabetes mellitus. The proportions for HDM allergy, hayfever, and asthma were 4.1% ($n = 7$), 10.0% ($n = 17$), and 2.9% ($n = 5$), respectively.

Subjects with and without respiratory allergies were compared with respect to selected general and dental characteristics (Table 1). Among subjects with respiratory allergies, 18.8% of the tooth surfaces had AL > 3 mm, whereas 36% of the surfaces had AL > 3 mm in subjects without allergies. Furthermore, subjects with allergies had a lower mean AL, and more teeth than subjects without allergies, but the latter result nar-

rowly missed statistical significance ($p = 0.06$).

Multivariable analyses using AL > 3 mm revealed that the extent of AL was inversely associated with the risk of respiratory allergies (Table 2). The full model showed that individuals with severe AL [OR 0.06 (95% CI 0.01–0.39), $p < 0.01$], moderate AL [OR 0.14 (95% CI 0.03–0.63), $p = 0.01$], and mild AL [OR 0.32 (95% CI 0.09–1.08), $p = 0.07$] had a lower risk of respiratory allergies compared to subjects with healthy periodontal conditions. This result was confirmed by an analysis using the percentage of surfaces with AL > 3 mm as a continuous variable [OR 0.96 (95% CI 0.94–0.99), per %, $p_{\text{trend}} < 0.01$].

A sensitivity analysis was run restricted for subjects younger than 60 years because of the low number of teeth in older subjects. Also, in this subpopulation, individuals with severe AL [OR 0.03 (95% CI < 0.01 –0.29), $p < 0.01$], moderate AL [OR 0.18 (95% CI 0.04–0.78), $p = 0.02$], and mild AL [OR 0.42 (95% CI 0.13–1.42), $p = 0.17$] had a lower risk of respiratory allergies than subjects with healthy periodontal conditions.

We performed further analyses using the mean AL over all assessed teeth as an alternative exposure variable. Subjects were again categorized into four groups (healthy periodontal conditions,

mild, moderate, and severe AL) according to the quartiles of distribution. These analyses showed again that subjects with severe AL had the lowest risk of respiratory allergies [OR 0.07 (95% CI 0.01–0.44), $p < 0.01$], followed by subjects with moderate AL [OR 0.18 (95% CI 0.04–0.76), $p = 0.02$] and mild AL [OR 0.43 (95% CI 0.13–1.39), $p = 0.16$] in comparison to individuals with healthy periodontal conditions. Also, an analysis performed with mean AL as a continuous variable confirmed these results [OR 0.54 (95% CI 0.34–0.86), per mm, $p_{\text{trend}} < 0.01$].

Furthermore, analysis was run using a different smoking categorization. The former and current smokers were further divided separately into two groups according to the number of cigarettes smoked per day (< 15 ; ≥ 15 cigarettes/day). This analysis also confirmed the main result of an inverse association between periodontitis and respiratory allergies.

Analyses with caries as independent variables were performed to verify the specificity of our findings to periodontitis. Adjusted for sex, age, and smoking, no association between DMFT [reference: low; mild, OR 1.23 (95% CI 0.30–5.00); moderate, OR 0.79 (95% CI 0.20–3.11); and high, OR 0.93 (95% CI 0.21–4.14)] as well as DMFS [reference: low; mild, OR 0.87 (95% CI 0.22–3.52); moderate, OR 1.90 (95% CI 0.50–7.13); and high, OR 0.35 (95% CI 0.05–2.32)] and respiratory allergies was found.

Table 1. Selected characteristics among subjects with and without respiratory allergies

Characteristics	Subjects without respiratory allergies ($n = 148$)	Subjects with respiratory allergies ($n = 22$)	p^*
Female (%)	46.6	40.9	0.65
Age (years)	37.1 (1.1)	37.5 (2.5)	0.77
School education (%)			0.57
≤ 10 years	79.1	86.4	
> 10 years	20.9	13.6	
Smoking (%)			0.39
Never-smoker	30.4	45.4	
Ex-smoker	25.0	18.2	
Current-smoker	44.6	36.4	
Alcohol consumption (%)			0.75
Low	85.1	81.8	
High	14.9	18.2	
Chronic bronchitis (%)	5.4	4.6	1.00
Positive family history for allergies or asthma (%)	12.7	18.2	0.50
Number of teeth	23 (0.4)	25 (0.9)	0.06
Attachment loss (mm)	2.31 (0.13)	1.56 (0.26)	0.03
Attachment loss > 3 mm (% of sites)	36.0 (2.5)	18.8 (4.3)	0.02
Diabetes duration (years)	14.8 (0.8)	18.1 (2.9)	0.48
Haemoglobin A1c (%)	7.8 (0.1)	7.7 (0.2)	0.86

Continuous data are given as mean (standard error), nominal data are given as percentages.

*Fisher's exact test (nominal data) or Mann-Whitney U -test (interval data).

Discussion

The present analysis confirmed our hypothesis of an inverse association between periodontitis and respiratory allergies in patients with type 1 diabetes mellitus. The risk of respiratory allergies decreased with increased AL. These results not only confirmed previous findings reported from the general adult population of West Pomerania (Friedrich et al. 2006), but also extended current knowledge by the finding that the inverse association between periodontitis and respiratory allergies was stronger in patients with type 1 diabetes mellitus than in subjects randomly selected from the general population [reference: healthy; mild AL, OR 0.93 (95% CI 0.69–1.24); moderate AL, OR 0.85 (95% CI 0.61–1.18); and severe AL, OR 0.56 (95% CI 0.36–0.86)] (Friedrich et al. 2006). An interplay

Table 2. The periodontitis-related risk of respiratory allergies

Effect*	Respiratory allergies	
	OR (95% CI)†	<i>p</i>
Unadjusted		
Attachment loss > 3 mm (reference: healthy)		
Mild	0.54 (0.18–1.63)	0.27
Moderate	0.35 (0.10–1.21)	0.10
Severe	0.17 (0.03–0.81)	0.03
	<i>p</i> _{trend} = 0.02	
Adjusted for sex and age		
Attachment loss > 3 mm (reference: healthy)		
Mild	0.43 (0.13–1.37)	0.15
Moderate	0.19 (0.04–0.80)	0.02
Severe	0.08 (0.01–0.47)	<0.01
	<i>p</i> _{trend} <0.01	
Adjusted for the full model‡		
Attachment loss > 3 mm (reference: healthy)		
Mild	0.30 (0.08–1.07)	0.06
Moderate	0.12 (0.02–0.60)	0.01
Severe	0.05 (0.01–0.35)	<0.01
	<i>p</i> _{trend} <0.01	

OR, odds ratios; CI, confidence intervals.

*Periodontal status was formed by dividing participants into four groups according to attachment loss > 3 mm: healthy, 0–7.6%; low, 7.6–27.0%; moderate, 27.1–54.2%; severe, > 54.2%.

†Logistic regression analyses.

‡Full model includes sex, age, smoking, and diabetes duration.

between type 1 diabetes mellitus, periodontal diseases, and respiratory diseases provides the most plausible explanation for these results. Several studies reported that patients with type 1 diabetes mellitus have an increased risk of periodontal disease (Genco 1996, Kinane & Chestnutt 1997) and a higher extent of periodontitis (Grossi et al. 1994, Firatli 1997, Lalla et al. 2006) compared to subjects without diabetes mellitus. Furthermore, it has been demonstrated that children with type 1 diabetes mellitus had fewer symptoms of asthma, hayfever, or eczema (Douek et al. 1999, Meerwaldt et al. 2002, Caffarelli et al. 2004) than healthy children. A meta-analysis (Cardwell et al. 2003) of 25 studies revealed a decreased asthma prevalence and a small non-significant reduction of the prevalence of eczema in patients with type 1 diabetes mellitus. In good agreement with these studies, we observed a slightly lower prevalence of respiratory allergies (12.9%) in the present study than in the general population (15.4%) (Friedrich et al. 2006) of the same catchment area. Lower proportions of allergies or allergic symptoms in patients with diabetes mellitus compared with healthy subjects have not always been confirmed (Stromberg et al. 1995, Stene & Nafstad 2001). One study found a

positive association between type 1 diabetes mellitus and symptoms of asthma (Stene & Nafstad 2001). Another study found no differences in the prevalence of respiratory diseases between children with type 1 diabetes mellitus and the reference population (Stromberg et al. 1995).

Periodontitis is an infection starting with the colonization of the oral cavity with periopathogenic microorganisms, in particular Gram-negative anaerobic bacteria in childhood (Umeda et al. 2004). Several studies found that patients with type 1 diabetes mellitus had an enhanced susceptibility to Gram-negative infections (Joshi et al. 1999) and periodontal pathogens (Loe 1993, Nishimura et al. 1998). The early infection with these periodontopathic bacteria may elicit an immune response (Bimstein et al. 2004) and promotes conditions for the onset of periodontal diseases in adult life. In the development of periodontal disease, different aetiological models are discussed (Yamazaki et al. 2003). The first model suggests that periodontitis is Th2-mediated and thus the activation of B-cells and secretion of interleukin 1 probably mediates tissue destruction. This model is supported by the finding of a decreased interferon- γ secretion in patients with periodontitis due to a decreased interferon- γ and interleukin-2

mRNA expression (Sigusch et al. 1998). This assumption receives further support by the detection of a decreased number of mast cells in chronic periodontitis tissue (Gemmell et al. 2004). A second model hypothesizes that the infection and the tissue destruction is caused by Th1 cells and interferon- γ , which stimulates the production of pro-inflammatory cytokines (Yamazaki et al. 2003). Two studies demonstrated that the mRNA expression of interferon- γ and interleukin-2 was increased in patients with chronic periodontitis (Ebersole & Taubman 1994, Takeichi et al. 2000). A third model links the Th1 and Th2 assumptions and proposes that both Th1 cells and Th2 cells are involved in the history of periodontal disease. Th1 cells are associated with stable lesions, whereas Th2 cells may be the major mediator in advanced and progressive periodontal lesions (Gemmell & Seymour 2004).

Possible explanations for inverse associations between infections (Th1-mediated) and allergic diseases (Th2-mediated), which has been displayed between tuberculosis, measles, or hepatitis A and allergic diseases (Shaheen et al. 1996, Matricardi et al. 1997, Shirakawa et al. 1997), are provided by the hygiene hypothesis and the Th1/Th2 paradigm (Mosmann & Coffman 1989, Romagnani 1992). There are, however, also conflicting results. For example, an inverse relation between a Th2-mediated infection by helminths and allergies in children (van den Biggelaar et al. 2000) has been reported.

The assessment of the severity and extent of periodontal disease is a matter of concern. The measurement of AL provides adequate information on the severity and extent of periodontitis, but the definition of periodontitis based on categorizations or different thresholds varies strongly between studies and need to be standardized (Burt 2005, Merchant & Pitiphat 2007). However, our results were consistent over numerous definitions of periodontitis (mean AL: categorized, continuous; percentage of surfaces with AL > 3 mm: categorized, continuous). Further, the specificity of our findings to periodontitis and the absence of an association between coronal caries and respiratory allergies argue against dominant confounding by socioeconomic status and health behaviour, which are related to both periodontitis and caries. The method for

defining respiratory allergies represents a limitation of the study, because self-report inherits the risk of recall bias. The interview included no standardized questionnaire for the ascertainment of hayfever, HDM allergy, and asthma. Furthermore, we had no information about current and past allergic or asthmatic symptoms. While a cross-sectional study like the present one is generally not suitable to prove causal relations, the biological plausibility of the association may indicate such a relation. Even though we were careful to adjust for possible confounding factors, further residual confounding cannot be unequivocally excluded.

In conclusion, there is a strong inverse association between periodontitis and respiratory allergies in patients with type 1 diabetes mellitus. The present study replicates findings from the general population and further supports the hygiene hypothesis.

Acknowledgement

The contributions to data collection made by field workers, study physicians, ultrasound technicians, interviewers, and computer assistants are gratefully acknowledged.

References

- Bimstein, E., Sapir, S., Hour-Haddad, Y., Dibart, S., Van Dyke, T. E. & Shapira, L. (2004) The relationship between *Porphyromonas gingivalis* infection and local and systemic factors in children. *Journal of Periodontology* **75**, 1371–1376.
- Burt, B. (2005) Position paper: epidemiology of periodontal diseases. *Journal of Periodontology* **76**, 1406–1419.
- Caffarelli, C., Cavagni, G., Pierdomenico, R., Chiari, G., Spattini, A. & Vanelli, M. (2004) Coexistence of IgE-mediated allergy and type 1 diabetes in childhood. *International Archives of Allergy and Immunology* **134**, 288–294.
- Cardwell, C. R., Shields, M. D., Carson, D. J. & Patterson, C. C. (2003) A meta-analysis of the association between childhood type 1 diabetes and atopic disease. *Diabetes Care* **26**, 2568–2574.
- Douek, I. F., Leech, N. J., Gillmor, H. A., Bingley, P. J. & Gale, E. A. (1999) Children with type-1 diabetes and their unaffected siblings have fewer symptoms of asthma. *Lancet* **353**, 1850.
- Ebersole, J. L. & Taubman, M. A. (1994) The protective nature of host responses in periodontal diseases. *Periodontology 2000* **5**, 112–141.
- Firatli, E. (1997) The relationship between clinical periodontal status and insulin-dependent diabetes mellitus. Results after 5 years. *Journal of Periodontology* **68**, 136–140.
- Friedrich, N., Volzke, H., Schwahn, C., Kramer, A., Junger, M., Schafer, T., John, U. & Kocher, T. (2006) Inverse association between periodontitis and respiratory allergies. *Clinical and Experimental Allergy* **36**, 495–502.
- Gemmell, E., Carter, C. L. & Seymour, G. J. (2004) Mast cells in human periodontal disease. *Journal of Dental Research* **83**, 384–387.
- Gemmell, E. & Seymour, G. J. (2004) Immunoregulatory control of Th1/Th2 cytokine profiles in periodontal disease. *Periodontology 2000* **35**, 21–41.
- Genco, R. J. (1996) Current view of risk factors for periodontal diseases. *Journal of Periodontology* **67**, 1041–1049.
- Grossi, S. G., Zambon, J. J., Ho, A. W., Koch, G., Dunford, R. G., Machtei, E. E., Norderyd, O. M. & Genco, R. J. (1994) Assessment of risk for periodontal disease. I. Risk indicators for attachment loss. *Journal of Periodontology* **65**, 260–267.
- Joshi, N., Caputo, G. M., Weitekamp, M. R. & Karchmer, A. W. (1999) Infections in patients with diabetes mellitus. *New England Journal of Medicine* **341**, 1906–1912.
- Kinane, D. F. & Chestnutt, I. G. (1997) Relationship of diabetes to periodontitis. *Current Opinion in Periodontology* **4**, 29–34.
- Lalla, E., Cheng, B., Lal, S., Tucker, S., Greenberg, E., Golland, R. & Lamster, I. B. (2006) Periodontal changes in children and adolescents with diabetes: a case-control study. *Diabetes Care* **29**, 295–299.
- Loe, H. (1993) Periodontal disease. The sixth complication of diabetes mellitus. *Diabetes Care* **16**, 329–334.
- Matricardi, P. M., Rosmini, F., Ferrigno, L., Nisini, R., Rapicetta, M., Chionne, P., Stroffolini, T., Pasquini, P. & D'Amelio, R. (1997) Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* **314**, 999–1003.
- Meerwaldt, R., Odink, R. J., Landaeta, R., Aarts, F., Brunekreef, B., Gerritsen, J., Van Aalderen, W. M. & Hoekstra, M. O. (2002) A lower prevalence of atopy symptoms in children with type 1 diabetes mellitus. *Clinical and Experimental Allergy* **32**, 254–255.
- Merchant, A. T. & Pitiphat, W. (2007) Researching periodontitis: challenges and opportunities. *Journal of Clinical Periodontology* **34**, 1007–1015.
- Mosmann, T. R. & Coffman, R. L. (1989) TH1 and TH2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annual Review of Immunology* **7**, 145–173.
- Nishimura, F., Takahashi, K., Kurihara, M., Takashiba, S. & Murayama, Y. (1998) Periodontal disease as a complication of diabetes mellitus. *Annals of Periodontology* **3**, 20–29.
- Romagnani, S. (1992) Human TH1 and TH2 subsets: regulation of differentiation and role in protection and immunopathology. *International Archives of Allergy and Immunology* **98**, 279–285.
- Shaheen, S. O., Aaby, P., Hall, A. J., Barker, D. J., Heyes, C. B., Shiell, A. W. & Goudiaby, A. (1996) Measles and atopy in Guinea-Bissau. *Lancet* **347**, 1792–1796.
- Shirakawa, T., Enomoto, T., Shimazu, S. & Hopkin, J. M. (1997) The inverse association between tuberculin responses and atopic disorder. *Science* **275**, 77–79.
- Sigusch, B., Klinger, G., Glockmann, E. & Simon, H. U. (1998) Early-onset and adult periodontitis associated with abnormal cytokine production by activated T lymphocytes. *Journal of Periodontology* **69**, 1098–1104.
- Stene, L. C. & Nafstad, P. (2001) Relation between occurrence of type 1 diabetes and asthma. *Lancet* **357**, 607–608.
- Strachan, D. P. (1989) Hay fever, hygiene, and household size. *BMJ* **299**, 1259–1260.
- Stromberg, L. G., Ludvigsson, G. J. & Bjorksten, B. (1995) Atopic allergy and delayed hypersensitivity in children with diabetes. *Journal of Allergy and Clinical Immunology* **96**, 188–192.
- Takeichi, O., Haber, J., Kawai, T., Smith, D. J., Moro, I. & Taubman, M. A. (2000) Cytokine profiles of T-lymphocytes from gingival tissues with pathological pocketing. *Journal of Dental Research* **79**, 1548–1555.
- Umeda, M., Miwa, Z., Takeuchi, Y., Ishizuka, M., Huang, Y., Noguchi, K., Tanaka, M., Takagi, Y. & Ishikawa, I. (2004) The distribution of periodontopathic bacteria among Japanese children and their parents. *Journal of Periodontal Research* **39**, 398–404.
- van den Biggelaar, A. H., van Ree, R., Rodrigues, L. C., Lell, B., Deelder, A. M., Kremsner, P. G. & Yazdanbakhsh, M. (2000) Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. *Lancet* **356**, 1723–1727.
- World Health Organization (1997) *Oral Health Surveys: Basic Methods*, 4th edition. Geneva: World Health Organization.
- Yamazaki, K., Yoshie, H. & Seymour, G. J. (2003) T cell regulation of the immune response to infection in periodontal diseases. *Histology and Histopathology* **18**, 889–896.

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Clinical Relevance

Scientific rationale for the study: To expand our knowledge on the systemic effects of periodontitis on systemic diseases, we studied the association between periodontal dis-

ease and allergy on the background of the hygiene hypothesis.

Principal findings: We observed that subjects without periodontitis had a higher chance of having an allergy than subjects with periodontitis. The

more advanced the periodontitis, the smaller the chance of having an allergy.

Practical implications: Pathways linking allergy and periodontitis should be studied further.