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Consensus Report

Advances in the progression of periodontitis and proposal of definitions of a periodontitis case and disease progression for use in risk factor research

Group C Consensus report of the 5th European workshop in periodontology

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Analytical Epidemiology of Periodontitis (Borrell & Papapanou 2005)

This group reviewed the analytical epidemiology of periodontitis, focussing on the 10-year period since the 1996 World Workshop on Periodontology (Papapanou 1996). Periodontal manifestations of systemic diseases as defined in the 1999 International Classification Workshop (Kinane 1999) were not considered.

In the discussion of risk factors, the group adhered to the risk assessment approach of Beck (1994), according to which, a true risk factor must fulfill the following four steps:

1. *Identification*, i.e. statistically significant odds ratio >1.0 in cross-sectional investigations;
2. *Retention of significance and direction of effect* in a multi-factorial model including other exposures as covariates;
3. *Assessment*, i.e. successful external validation of the model in independent populations;
4. *Targeting step*, i.e. proof that intervention strategies targeted at the factor reduce the incidence of the disease.

It is recognized that currently non-modifiable risk factors (e.g. genetic polymorphisms) cannot fulfill the fourth step.

The group identified a number of issues that impact upon data interpretation, the most significant ones being the following:

- Case definition;
- Disease onset *versus* progression; and
- Incomplete risk assessment.

There is a lack of uniformity within the literature with respect to the criteria used to define a ''case'' of periodontitis. Calculations of odds ratios or relative risk require dichotomization of the outcome variable and are therefore dependent upon the thresholds used to define ''disease''. Consequently, a substantial part of the variation in odds ratios can be attributed to inconsistency in utilization of thresholds, rendering data interpretation difficult.

With a few exceptions, the literature has not specifically addressed the possibility that risk factors responsible for the onset of periodontitis may differ from those responsible for determining disease progression. This is an important distinction, because intervention strategies aimed at risk factors for disease onset (primary prevention strategies) may not be of benefit in controlling disease progression (secondary prevention).

There is a plethora of association studies in which *putative* risk factors have been shown to fulfill the identification step (first step) of the risk assessment process. A number of such factors have been shown to fulfill the second step, by confirming their significance in multi-factorial models, employing relevant covariates. The consistency of these associations in independent populations has been confirmed for a small number of factors. There is a general

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lack of adequately designed studies addressing the ''targeting step'' of the risk assessment process and therefore the majority of factors currently studied remain in the ''putative risk factor'' category (Table 1).

The group considered that the targeting step has, in part, been indirectly fulfilled for the three factors categorized as ''established'' risk factors. For example, suppression of specific bacteria following treatment has been associated with disease resolution in several studies, although it must be recognized that this approach does not exclusively target specific species. Treatment studies have consistently demonstrated inferior therapeutic outcomes in current smokers relative to former or never smokers. Longitudinal observation studies have demonstrated reduced tooth loss and lower incidence of periodontal disease progression in smokers who have quit. However, the decision to stop smoking does not lend itself to traditional randomized-controlled trial designs. Similarly, treatment studies of patients with diabetes mellitus have shown an association between poor metabolic control (HbA1c) and sub-optimal treatment outcome, but for smoking cessation the design of randomized intervention studies remains problematic.

Given the limitations inherent within association studies to ascribe risk, the risk assessment process for the currently classified putative risk factors requires further studies addressing steps two through four of the risk assessment model. While a consensus exists for a genetic basis for susceptibility to periodontitis, the study of individual genetic determinants must expand beyond the univariate associations to include interaction with other covariates (e.g. specific bacteria, smoking or other gene polymorphisms). Redundancy within the human genome and downstream effects on phenotypic expression should also be considered.

Table 1.

Established risk factors	Putative risk factors
Specific plaque bacteria	Gene polymorphisms
Smoking	Age
Diabetes (poorly controlled)	Socio-economic status
	Race/ethnicity
	Gender
	Psychosocial factors
	Osteoporosis/osteopenia
	Obesity

The traditional approach to controlling periodontitis over the last 40 years has focused primarily upon non-specific anti-microbial strategies and has achieved limited success in reducing the prevalence and incidence of the more advanced forms periodontitis. Given the importance of the host response to the plaque biofilm in disease aetiology and progression and the demonstrable effects of smoking upon periodontal as well as systemic health, adding periodontal components to intervention studies exploring the impact of smoking cessation will provide important information.

Identification of Genetic Risk Factors for Periodontitis (Loos et al. 2005)

This group recognizes the importance of genetic factors in the susceptibility and progression of periodontitis based to a large extent on studies of familial aggregation and studies on twins. The literature was reviewed for evidence of genetic risk factors involved in the susceptibility to and severity of periodontitis. A candidate gene approach has been used in attempts to identify modifying disease genes in other forms of periodontitis. A multitude of polymorphisms in genes, most of which code aspects of the host immune response, have been explored. There are indications that some polymorphisms in the IL1 cluster, the Fcγ and vitamin-D receptor genes may be associated with periodontitis in certain populations. However, in general, the studies appear underpowered and do not adequately take into account other pertinent risk factors. Future studies should include large cohorts, should adequately control for other risk factors and should employ modern biological and medical bio-informatics. Linkage analysis in multiplex families with a definite disease phenotype should be initiated as an alternative to the candidate gene approach. Other alternatives include the study of gene expression signatures and genome wide screening.

Mechanisms of Action of Environmental Factors – Cigarette Smoking (Palmer et al. 2005)

Most of the current evidence identifying tobacco smoking as a risk factor for periodontitis relates to cigarette smoking. The detrimental effects result mainly from long-term chronic systemic exposure to tobacco combustion products absorbed in the lungs.

Plaque levels in smokers are not significantly increased, but there are suggestions of increased prevalence and/or proportions of suspected periodontal pathogens. Bleeding scores are suppressed in smokers and increase in subjects who quit smoking. In addition, leucocyte functions are impaired, shifting the balance of their activities towards tissue destruction.

The effects on T- and B-cell functions and on antibody levels are mainly suppressive. As individual components of cigarette smoke might have varying immunosuppressive or immuno-stimulatory effects, the net effect depends upon dose and duration of exposure to these molecules.

The resting gingival crevicular fluid (GCF) flow rate is reduced in cigarette smokers, and, during experimental gingivitis, the increase in GCF flow rate is smaller. An episode of smoking may produce a transient increase in GCF flow rate, thereby affecting GCF levels of inflammatory markers.

Most studies on gingival and periodontal fibroblasts used *in vitro* assays with high nicotine levels and omitted to test the effects of a multitude of other noxious compounds in cigarette smoke. Impaired proliferation, attachment and collagen production occurred in combination with increased cytotoxicity and collagenase activity. Although the in vivo potential of these effects cannot be estimated, cigarette smoke products most likely affect fibroblast recruitment and adhesion to root surfaces.

Given the profound effects of cigarette smoking on inflammatory and immune mechanisms, studies on molecular mechanisms of periodontitis must account for the smoking status of the subject.

It is likely that genetic factors influence the interaction between cigarette smoking, the host and the bacterial challenge.

Prediction of Periodontitis Progression (Heitz-Mayfield 2005)

While bacteria are the primary aetiological factors in the initiation of periodontitis, a range of host-related factors influence periodontitis progression.

There is substantial evidence in longitudinal studies for a number of individual predictors of periodontitis progression, several of which could be useful in clinical practice. Cigarette smoking is a strong predictor of periodontitis progression, the effect of which is dose related. Therefore smoking status must be incorporated in the risk assessment of the patient. Diabetic patients need to be assessed with respect to their glycaemic control as evidence shows that poorly controlled diabetics have an increased risk for disease progression. There is evidence that patients infected with specific bacteria demonstrate a greater risk for disease progression. A patient-based microbial evaluation may be helpful for individual risk assessment.

Although studies have demonstrated an association between genetic polymorphisms and periodontitis, the data are inconclusive, and genotyping alone cannot as yet be used to identify individuals at risk for periodontitis progression.

Longitudinal studies of periodontitis have shown that the severity and extent of baseline disease and tooth loss can be useful to predict further progression of the disease. A number of clinical factors assessed at the patient level such as bleeding on probing and probing depth greater or equal to 6 mm at re-evaluation can be used to identify patients at risk for disease progression.

If factors that individually are shown to be associated with disease progression are combined in a multifactorial model, this may improve the ability to predict disease progression. A number of multifactorial models for risk assessment at the subject level have been developed. Although there is currently limited data to support these models, they may prove to be useful.

Criteria for Defining a ''Periodontitis Case'' and ''Disease Progression'' to be Used in Epidemiological Studies of Risk Factors

Setting the context

Based on the existing literature on risk factors for periodontitis, it is not possible to ascertain whether the reported variance in odds ratios or relative risk is because of a varying biological impact of the factor under investigation in different populations or merely reflects the inconsistency in case definitions or thresholds for progression used across studies. In order to establish a framework that allows some consistency of data interpretation across global epidemiological studies, it is necessary for all studies to use one consistent definition for ''a periodontitis case'' and ''periodontitis progression''. Such an approach allows odds ratios and estimates of relative risk, both of which are sensitive to threshold definition, to be derived that are directly comparable between different studies. This does not restrict the use of additional case definitions/progression thresholds to address other issues related to the specific aims of individual studies. In this context it is important to recognize that:

1. Periodontitis cannot be reflected by measurements of a single variable. While past experience of periodontitis is reflected by attachment loss/bone loss measurements, assessment of disease presence requires additional measurement of bleeding on probing and/or probing pocket depth.
2. The accepted measure of cumulative lifetime experience of periodontitis is attachment loss, therefore this measure should be the primary outcome variable used in studies of risk factors for periodontitis.

Proposed criteria for a two-level periodontitis case definition

1. Presence of proximal attachment loss of $\geqslant 3$ mm in $\geqslant 2$ non-adjacent teeth.
2. Presence of proximal attachment loss of $\geqslant 5$ mm in $\geqslant 30\%$ of teeth present.

Rationale for definition of periodontitis case

- Two threshold levels are proposed: the first to enable the utilization of a sensitive case definition (inclusive of incipient cases) and the second to allow a more specific case definition (to identify only cases with substantial extent and severity).
- Proximal sites and non-adjacent teeth are specified, in order to minimize the likelihood of including attachment loss affecting buccal/lingual sites or adjacent inter-dental sites for reasons other than periodontitis.
- The 3 mm threshold is based upon studies of incremental attachment loss measurement, where the error of the recording method was calculated at 2.5 mm.
- The proposed criteria are not designed for the assessment of prevalence of periodontitis across populations and/or age groups; the focus is to identify risk factors.

Analytical Strategy

The group proposes that:

- The exposure of interest, along with relevant covariates including age, is used in two separate multi-factorial models, using the ''periodontitis case'' as defined in each of the two case definitions as the dependent variable. Adjusted odds ratios and 95% confidence limits should be reported.
- The impact of the putative risk factor on the extent of periodontitis (percentage of teeth affected according to the above criteria) is examined to investigate a dose-response effect, using a new multivariate model. This is applied for each of the two severity levels.
- Additional models may be developed as needed to test specific hypotheses. For example, to examine the effect of the putative risk factor on current disease status, a model that incorporates a composite case definition that includes a combination of attachment loss and measures of current disease status (presence of BOP, PPD exceeding a set threshold) can be developed.

Proposed criteria for periodontitis progression case definition

- Presence of $\geqslant 2$ teeth demonstrating a longitudinal loss of proximal attachment of $\geqslant 3$ mm. In situations where serial proximal attachment level measurements are not available, longitudinal radiographic bone loss of $\geqslant 2$ mm at $\geqslant 2$ teeth may be used as a substitute.

Rationale for definition of a case of periodontitis progression

- The threshold for periodontitis progression is based upon extensively documented evidence within the periodontal literature.

- The threshold is set at the level of two teeth to minimize the risk of including cases of progression arising because of reasons other than periodontitis.

Analytical Strategy

The group proposes that:

- The exposure of interest, along with relevant covariates including age, is used in a multi-factorial model, using the ''case'' as the dependent variable. Adjusted odds ratios and/or relative risk estimates as well as 95% confidence limits should be reported.
- The impact of the putative risk factor on the extent of periodontitis progression (percentage of teeth affected by disease progression) is examined to investigate a dose-response effect, using a new multivariate model.
- Additional models may be developed as needed to test specific hypotheses.

The group recognizes the limitations of the proposed guidelines but, if implemented, they will facilitate global comparisons between future analytical epidemiological studies of periodontitis.

These guidelines have been approved by the plenum session of the 5th European Workshop on Periodontology.

References

Beck, J. D. (1994) Methods of assessing risk for periodontitis and developing multifactorial models. *Journal of Periodontology* **65** (Suppl.), 468–478.

Borrell, L. N. & Papapanou, P. N. (2005) Analytical epidemiology of periodontitis. *Journal of Clinical Periodontology* **32**, (Suppl. 6), 132–158.

Heitz-Mayfield, L. J. A. (2005) Disease progression: identification of high risk groups and individuals for periodontitis. *Journal of Clinical Periodontology* **32**, (Suppl. 6), 196–209.

Kinane, D. F. (1999) Periodontitis modified by systemic factors. *Annals of Periodontology* **4**, 54–64.

Loos, B. G., John, R. P. & Laine, M. L. (2005) Identification of genetic risk factors for periodontitis and possible mechanisms of action. *Journal of Clinical Periodontology* **32**, (Suppl. 6), 159–179.

Palmer, R. M., Wilson, R. F., Hasan, A. S. & Scott, D. (2005) Mechanism of action of environmental factors. Tobacco smoking. *Journal of Clinical Periodontology* **32**, (Suppl. 6), 180–195.

Papapanou, P. N. (1996) Periodontal diseases: epidemiology. *Annals of Periodontology* **1**, 1–36.

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