I.  EPIDEMIOLOGY OF PERIODONTAL DISEASES
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The term epidemiology is of Hellenic origin. It consists of the preposition “epi”, which means “among” or “against”, and the noun “demos” which means “people”. As denoted by its etymology, epidemiology is defined as “the study of the distribution of disease or a physiological condition in human populations and of the factors that influence this distribution” (Lilienfeld, 1978).

The information obtained from an epidemiologic investigation should extend beyond a mere description of the disease in different populations (1) (descriptive epidemiology). It should be further expanded to:

(2) elucidate the etiology of a specific disease by combining epidemiologic data with information from other disciplines such as genetics, biochemistry, microbiology, sociology, etc. (etiologic epidemiology);

(3) evaluate the consistency of epidemiologic data with hypotheses developed clinically or experimentally (analytical epidemiology); and

(4) provide the basis for developing and evaluating preventive procedures and public health practices (experimental/intervention epidemiology).

Epidemiological research in periodontology must:

(1) fulfill the task of providing data on the prevalence of periodontal diseases in different populations, i.e. the frequency of their occurrence, as well as on the severity of such conditions, i.e. the level of occurring pathologic changes;

(2) elucidate aspects related to the etiology and the determinants of development of these diseases (causative and risk factors); and

(3) provide documentation concerning the effectiveness of preventive and therapeutic measures aimed against these diseases on a population basis.

Methodological issues. Examination methods – index systems in epidemiology

Examination of the periodontal status for epidemiological purposes of a given individual includes clinical assessments of inflammation in the periodontal tissues, recording of probing depths and clinical attachment levels and radiographic assessments of supporting alveolar bone. A variety of index systems for the scoring of these parameters has been developed over the years.
Some of these systems were designed exclusively for examination of patients in a dental practice set-up, while others were developed in order to be utilized in epidemiologic research.

**Assessment of inflammation of the periodontal tissues**

Presence of inflammation in the marginal portion of the gingiva is usually recorded by means of probing assessments, according to the principles of the *Gingival Index* outlined in the publication by Löe (1967). According to this system:

<table>
<thead>
<tr>
<th>Code 0</th>
<th>Normal gingiva</th>
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<tbody>
<tr>
<td>Code 1</td>
<td>Mild inflammation. Slight change in colour, slight oedema. No bleeding on probing</td>
</tr>
<tr>
<td>Code 2</td>
<td>Moderate inflammation. Redness, oedema and glazing. Bleeding on probing</td>
</tr>
<tr>
<td>Code 3</td>
<td>Severe inflammation. Marked redness and oedema, ulceration. Spontaneous bleeding</td>
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**Bleeding on probing** to the base of the probable pocket has been a common way of assessing presence of *subgingival inflammation* (Mühlemann & Son, 1971). In this dichotomous registration, 1 is scored in cases where bleeding emerges within 15 seconds after probing and 0 is scored in cases without bleeding. Presence/absence of bleeding on probing to the base of the pocket is increasingly tending to substitute the use of the Gingival Index in epidemiologic studies.

**Assessment of loss of periodontal tissue support**

In contemporary epidemiologic studies, loss of periodontal tissue support is assessed by measurements of pocket depth and attachment level. Probing pocket depth (PPD) is defined as
the distance from the gingival margin to the location of the tip of a periodontal probe inserted in the pocket with moderate probing force. Clinical attachment level (CAL) is defined as the distance from the cemento-enamel junction (CEJ) to the location of the inserted probe tip. Probing assessments may be carried out at different locations of the tooth circumference (buccal, lingual, mesial or distal sites). The number of probing assessments per tooth has varied in epidemiologic studies from two to six, while the examination may either include all present teeth (full-mouth) or a subset of index teeth (partial-mouth examination).

(a) Clinical attachment loss (CAL) and probing depth (PD).
(b) CAL and recession.


Radiographic assessment of alveolar bone loss

Radiographs have been commonly employed in cross-sectional epidemiologic studies to evaluate the result of periodontal disease on the supporting tissues and are thought to provide valid estimates of the extent and severity of destructive periodontitis. Radiographic assessments have been particularly common as screening methods for detecting subjects suffering from juvenile periodontitis as well as a means for monitoring periodontal disease progression in longitudinal studies. Assessments of bone loss in intraoral radiographs are usually performed by evaluating a multitude of qualitative and quantitative features of the visualized interproximal bone:
(1) presence of an intact lamina dura,
(2) the width of the periodontal ligament space,
(3) the morphology of the bone crest (“even” or “angular” appearance), and
(4) the distance between the CEJ and the most coronal level at which the periodontal ligament space is considered to retain a normal width.

The threshold for bone loss, i.e. the CEJ – bone crest distance considered to indicate that bone loss has occurred is above 2 mm.

Radiographic data are usually presented as
(1) mean bone loss scores per subject (or group of subjects), and
(2) number or percentage of tooth surfaces per subject (or group of subjects) exhibiting bone loss exceeding certain thresholds.

In some studies, bone loss was frequently recorded, describing the amount of lost or remaining bone as a percentage of the length of the root or the tooth.

Assessment of periodontal treatment needs

An index system aimed at assessing the need for periodontal treatment in large population groups was developed, at the initiative of the World Health Organization (WHO), by Ainamo et al. (1982). The principles of the Community Periodontal Index of Treatment Needs (CPITN) can be summarized as follows:
1. The dentition is divided into six sextants (one anterior and two posterior tooth regions in each dental arch). The treatment need in a sextant is recorded when two or more teeth, not intended for extraction, are present. If only one tooth remains in the sextant, the tooth is included in the adjoining sextant.

2. Probing assessments are performed either around all teeth in a sextant or around certain index teeth. However, only the most severe measure in the sextant is chosen to represent the sextant.

3. The periodontal conditions are scored as follows:
- **Code 1** is given to a sextant with no pockets, calculus or overhangs of fillings but in which bleeding occurs after gentle probing in one or several gingival units.
- **Code 2** is assigned to a sextant if there are no pockets exceeding 3 mm, but in which dental calculus and plaque-retaining factors are seen or recognized subgingivally.
- **Code 3** is given to a sextant that harbors 4–5 mm deep pockets.
- **Code 4** is given to a sextant that harbors pockets 6 mm deep or deeper.

4. The treatment needs are scores based on the most severe code in the dentition as:
- TN 0, in case of gingival health,
- TN 1 indicating need for improved oral hygiene if code 1 has been recorded,
TN 2 indicating need for scaling, removal of overhangs, and improved oral hygiene (codes 2 + 3) 
TN 3 indicating complex treatment (code 4).

Although not designed for epidemiological purposes, this index system has been 
extensively used worldwide, and CPITN-based studies have often been the exclusive source of 
epidemiologic information on periodontal conditions.

**Frequency distribution of periodontal diseases**

Advanced periodontal disease was not evenly distributed in the population and not readily 
correlated to supragingival plaque levels; instead, the majority of the subjects examined exhibited 
light periodontal problems while a limited group was affected by advanced disease.

Current evidence suggests that the prevalence of severe periodontitis is not uniformly 
distributed among various races, ethnicities, or socioeconomic groups.

- 15 132 adults: CAL 
  - 99% youngest (18–24 
    years) had CAL ≥ 1 mm 
    on at least 1 tooth and 
    32.8% of sites 
  - 1.9% of youngest and 
    35% of oldest 
    (55–64 years) had more 
    severe CAL ≥ 5 mm 
  - 5.7% youngest 
    and 16.1% oldest had 
    pockets 4–6 mm 
  - < 0.1% youngest and 
    1.1% oldest had 
    pockets ≥ 7 mm

- More disease in blacks; 
  low education status

- Prevalence of periodontal disease*
  - at least 1 site with 
    CAL ≥ 5 mm and 1 site 
    with pocket ≥ 4 mm

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>1988–1994</th>
<th>1999–2004</th>
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<tr>
<td>20–34</td>
<td>8.48</td>
<td>3.84</td>
</tr>
<tr>
<td>35–49</td>
<td>15.73</td>
<td>10.41</td>
</tr>
<tr>
<td>50–64</td>
<td>21.87</td>
<td>11.88</td>
</tr>
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</table>

The prevalence of periodontitis based on:
(a) US national survey (representing population) data, 1985–86, and 
(b) US National Health and Nutrition Examination Surveys (NHANES) data, 1988–94 and 1999– 
Frequency distribution of various levels of severity of periodontal diseases


![Frequency distribution chart](image)

Frequency (%) distribution of individuals according to the severity of periodontal disease experience in 1973, 1983, 1993, and 2003. Total number of individuals in age groups 20–70. The proportion of individuals with advanced periodontitis (Group 5) remained unchanged.

Based on these data derived from a population with the best access to and utilization of oral health care in the world, we may conclude that the fraction of the population which is most susceptible to severe periodontitis is apparently not declining in frequency.

**Edentulism**

What was also well documented in these and other studies is that the rate of edentulism has decreased substantially over the past 30 years, with elderly groups retaining their natural dentition and higher mean numbers of teeth than their counterparts a generation ago. As a consequence, this fact per se should contribute to an increased prevalence of periodontal disease in older age cohorts, since retained teeth in the elderly are more likely to experience substantial cumulative attachment loss which forms the basis of the assessment of prevalence.

Relatively uniform criteria have been used in epidemiologic studies of aggressive periodontitis in young subjects (juvenile periodontitis – JP, and particularly the localized form –
localized juvenile periodontitis – LJP). In black subjects, the disease is more prevalent, probably at levels over 1%, and the sex ratio shows that males are affected more frequently than females. Smoking and low socioeconomic status have been confirmed to be associated with aggressive periodontitis in various populations.

**Risk factors for periodontitis**

There is an abundance of both empirical evidence and substantial theoretical justification for accepting the widespread belief that many diseases have more than one cause, i.e. that they are of multi-factorial etiology. In the case of most infectious diseases for example, it is known that the presence of the microbial agent (which we define as the necessary condition) is not always accompanied by signs or symptoms characteristic of that disorder. Thus, the agent itself is not sufficient to cause any pathologic occurrence; rather, the disease development may be dependent on multiple, diverse additional factors, including specific host responses, toxique exposures, nutritional deficiencies, emotional stress, and the complex impact of social influences. A distinction has to be drawn between a causal factor and a risk factor.

In a broad sense, the term risk factor may indicate an aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic which, on the basis of epidemiologic evidence, is known to be associated with disease-related conditions. Such an attribute or exposure may be associated with an increased probability of occurrence of a particular disease. A risk factor may be modified by intervention, thereby reducing the likelihood that the particular disease will occur.

Potential or putative risk factors (often also referred to as risk indicators) are first identified and thereafter tested until their significance as true risk factors is proven. Finally, distinction must be made between prognostic factors (or disease predictors), i.e. characteristics related to the progression of pre-existing disease and true risk factors, i.e. exposures related to the onset of the disease. For example, it is established in longitudinal studies of periodontal disease (Papapanou et al., 1989), that the amount of alveolar bone loss or the number of teeth present at baseline may be used to predict further progression of the disease. These variables are, in fact, alternative measures of the disease itself and express the level of susceptibility of a given subject to periodontal disease. Distinction is also made between putative factors that are not amenable to intervention (non-modifiable background factors) and modifiable factors (environmental, acquired, and behavioral).
Non-modifiable background factors

Age

The relationship between age and periodontitis is complex. Early evidence demonstrates that both the prevalence and severity of periodontitis increase with older age, suggesting that age may be a marker for periodontal tissue support loss. However, the concept of periodontitis as an inevitable consequence of ageing has been challenged over the years and the alleged ‘age effect’ likely represents the cumulative effect of prolonged exposure to true risk factors.

Gender

There is no established, inherent difference between men and women in their susceptibility to periodontitis, although men have been shown to exhibit worse periodontal health than women in multiple studies from different populations. This difference has been traditionally considered to be a reflection of better oral hygiene practices among women.

Race/Ethnicity

Differences in the prevalence of periodontitis between countries and across continents have been demonstrated. However, race/ethnicity is usually a social construct that determines opportunities related to access, status and resources.

Gene polymorphisms

Kornman et al. (1997) reported an association of a composite genotype based on specific polymorphisms in the interleukin-1 gene cluster with severe periodontitis in non-smokers. Similar work was quickly expanded to include the study of other gene polymorphisms such as the interleukin-1 receptor antagonist; interleukin-6; interleukin-10 etc. The majority of the cross-sectional studies report positive associations between the investigated polymorphisms and the extent or the severity of periodontitis. Lang et al. (2000) concluded that IL-1 genotype-positive subjects have a genetically determined hyper-inflammatory response that is expressed clinically in the periodontal tissues as increased prevalence and incidence of bleeding on probing during maintenance. There is insufficient epidemiologic evidence that convincingly establishes any of the above polymorphisms as true risk factors for periodontitis.

Environmental, acquired, and behavioral factors

Specific microbiota

The microbial etiology of gingivitis (Löe et al., 1965; Theilade et al., 1966) and periodontitis (Lindhe et al., 1973) has been established for several decades. Yet, epidemiologic
studies that systematically investigated the role of specific microbiota as risk factors for periodontitis were undertaken fairly recently. Based on the criteria for pathogenicity (Socransky, 1994), the consensus report of the 1996 World Workshop in Periodontics identified three species, *Actinobacillus actinomycetemcomitans* (Aggregatibacter actinomycetemcomitans), *Porphyromonas gingivalis*, and *Bacteroides forsythus* (*Tannerella forsythia*), as causative factors for periodontitis.

However, both the prevalence and the level of colonization by these pathogens have been shown to vary significantly between populations of different racial or geographic origin. Importantly, the association between high levels of colonization by specific periodontal pathogens and the progression of periodontal disease has been corroborated by longitudinal data in untreated populations.

**Cigarette smoking**

A substantial number of studies established the association of smoking to poor periodontal status. In longitudinal studies, smoking has been found to confer a statistically significant increased risk for periodontitis progression after adjustment for other covariates. Meta-analysis is a statistical method which combines results from different studies of similar design, in order to gain an overall increased power, i.e. an enhanced potential to reveal biological associations which may exist but are difficult to detect.
Figure (From Papapanou, 1996) describes a meta-analysis of data from studies studying the association between smoking and periodontal conditions. Bars indicate the 95% confidence limits for the depicted odds ratios.

Cigarette smoking appears to fulfill the majority of the required steps of the risk assessment process by Beck (1994) and is considered one of the major risk factors for periodontitis.

**Diabetes mellitus**

Diabetes as a risk factor for periodontitis has been debated for decades (Genco & Löe, 1993), but several biologically plausible mechanisms by which the disease may contribute to impaired periodontal conditions have been identified over the past decade. This association is especially pronounced in subjects with poor metabolic control and a long duration of the disease. Several studies suggest a two-way relationship between diabetes and periodontitis, with more severe periodontal tissue destruction in people with diabetes but also a poorer metabolic control.
of diabetes in subjects with periodontitis. The data strongly indicate that diabetes mellitus is one of the major risk factor for periodontitis.

**Obesity**

The biologic plausibility of a potential link between obesity and periodontitis has been suggested to involve a hyper-inflammatory state and an aberrant lipid metabolism prevalent in obesity, as well as the pathway of insulin resistance all of which may collectively result in an enhanced breakdown of the periodontal tissue support. Indeed, a number of recent studies point to a positive association between obesity, defined as body mass index (BMI) ≥30, and periodontitis.

**Osteopenia/Osteoporosis**

Several cross-sectional studies, of limited sample size and largely confined to postmenopausal women, have suggested that women with low bone mineral density are more likely to have CAL, gingival recession and/or pronounced gingival inflammation. However, studies that failed to report such an association have been published as well. It appears therefore that additional research is needed to unequivocally establish or refute the role of osteoporosis as a risk factor for periodontitis.

**Psychosocial factors**

The mechanisms by which psychosocial stress may affect the periodontal status are complex. It has been suggested that one of the plausible pathways may involve behavioral changes leading to smoking and poor oral hygiene that, in turn, may affect periodontal health. Nevertheless, given the established role of the sympathetic, parasympathetic, and the nervous systems, as well as that of the hypothalamic–pituitary–adrenal axis on brain to immune regulatory pathways, such a role is clearly biologically plausible.

**Summary**

Specific bacteria, cigarette smoking, and diabetes mellitus are the major established risk factors for periodontitis. A number of biologically plausible, potentially important additional factors are in need of further investigation in future studies to establish or refute as risk factors.
II. PERIODONTAL INFECTIONS AND RISK FOR SYSTEMIC DISEASE
Assoc. Prof. Theodora Bolyarova, MD

During the past 3 decades, an entirely new area of periodontal research has emerged, commonly referred to as “periodontal medicine”. Following some reports, a link between periodontal infections and a number of systemic conditions are exist. The biological plausibility of the proposed associations between periodontitis and atherosclerosis, cardiovascular and cerebrovascular disease, pregnancy complications, and diabetes mellitus, and the relevant epidemiological evidence available today are summarized. A wealth of data originating from diverse areas of investigation have implicated chronic, low-level inflammation as an important factor in atherosclerotic cardiovascular disease (CVD).

Periodontal diseases as a risk for cardiovascular disease.

An early study by DeStefano et al. (1993) found a nearly two-fold higher risk of CHD for individuals with periodontal disease. Circulating levels of several cytokines (IL-1 beta, IL-2, IL-6, and IL-8) induced during the course of several infections (Endo et al., 1992; Humar et al., 1999; Otto et al., 1999, Bolyarova et al., 2014), but also locally in the periodontal tissues in conjunction with periodontitis (Salvi et al., 1998), have been identified as biomarkers of cardiovascular disease (Hackam & Anand, 2003; Hansson, 2005). A number of studies have examined the presence of oral bacteria in atheromatic plaque lesions. A similar study using the polymerase chain reaction (Haraszthy et al., 2000) reported that 30% of the carotid endarterectomy specimens examined were positive for T. forsythia, 26% for P. gingivalis, 18% for A. actinomycetemcomitans, and 14% positive for Pr. intermedia.

In our study (T. Bolyarova, M. Marina, V. Tolchkov, B. Baev, 2014) for the first in Bulgaria a gene fragment has been amplified, encoding 16S rRNA with already described pair of primers in literature, designed for the 16S rRNA and specific for Porphyromonas gingivalis. P. gingivalis has been identified in 11 out of 54 studied dental plaque samples that belong respectively to 3 healthy individuals, 3 patients with SAP (stable angina pectoris) and 5 patients with ACS (acute coronary syndrome). P. gingivalis has been identified in 2 out of 10 atheromatous plaques. Our results support the hypothesis about a direct involvement of P. gingivalis into the pathogenetic mechanisms of atherosclerosis.
Poor periodontal status was significantly associated with:
- increased CRP;
- increased fibrinogen levels and
- higher carotid artery intima/media wall thickness.

The studies strongly suggest a biologically plausible association between periodontal infections and the pathogenesis of atherosclerotic cardiovascular disease. Obviously, studies that have failed to document such an association or that point to a possibility of a more complex, conditional relationship exist as well.

**Periodontitis as a risk for respiratory infections**

Beginning in 1992 with a report by Scannapieco’s group at SUNY-Buffalo (Scannapieco et al., 1992), several investigators have hypothesized that oral and/or periodontal infection may increase the risk for bacterial pneumonia or COPD (chronic obstructive pulmonary disease). Oral cavity may have a critical role in respiratory infections. Oral bacteria from the periodontal pocket can be aspirated into the lung to cause aspiration pneumonia. The teeth may also serve as a reservoir for respiratory pathogen colonization and subsequent nosocomial pneumonia. Also, periodontal disease associated enzymes in saliva may modify mucosal surfaces to promote adhesion and colonization by respiratory pathogens, which are then aspirated into the lungs. Cytokines originating from periodontal tissues may alter respiratory epithelium to promote infection by respiratory pathogens. Individuals with poor oral hygiene were at increased risk for chronic respiratory diseases such as bronchitis and emphysema. At present there is not sufficient evidence to say that there is an association between periodontal disease and COPD (Scannapieco et al., 2003; Azarpazhooh & Leake, 2006). There is emerging evidence for an association between hospital-acquired (nosocomial) bacterial pneumonia and periodontal disease.

**Pregnancy complications**

Preterm infants are born prior to completion of 37 weeks of gestation. A number of risk factors for preterm birth has been identified. These include young maternal age, multiple gestation, small weight gains during pregnancy, cervical incompetence, smoking, alcohol and drugs of abuse, black race, and a number of maternal infections. Importantly, approximately 50% of the variance in the incidence of preterm birth remains unexplained. The possibility that periodontal infections may constitute such maternal infections that adversely influence birth outcome was raised for the first time in the late 1980s (McGregor et al., 1988). Collins et al.
(1994) demonstrated that injection of *P. gingivalis* in the pregnant hamster resulted in intrauterine growth retardation, smaller fetuses, and an increase in proinflammatory mediators such as IL-1beta and PGE2 in the amniotic fluid. Multivariate logistic regression models, controlling for other risk factors and covariates, demonstrated that periodontitis, defined as ≥60% of all sites with attachment loss of ≥3 mm, conferred adjusted ORs of 7.9 for preterm, low birthweight babies (<2500g).

**Diabetes mellitus**

In line with the concept that infections may contribute to impaired metabolic control of diabetes, studies of both type 1 and type 2 diabetic subjects have indicated that periodontal infections may also be detrimental in this context. The proposed associations (of periodontal infections as risk factors for systemic disease) appear to be biologically plausible, but at this stage it is not possible to draw the magnitude of their biological effects. Nevertheless, studies underscore that the oral cavity is an integral part of the human body, and that systemic health must encompass oral, and periodontal, health as well.

Recently, long-term use of bone anti-resorptive agents, specifically **bisphosphonates**, has been associated with osteonecrosis of the jaw (ONJ) (Marx, 2003; Ruggiero et al., 2004). An increased incidence of ONJ has been observed after 36 months from the start of therapy in patients receiving zoledronic acid or pamidronate for the treatment of myeloma or breast cancer. This data also indicated that patients with prior dental problems might have a higher risk of ONJ. As the bisphosphonates are potent osteoclast inhibitors, their long-term use may suppress bone turnover and compromise healing of even physiological micro-injuries within bone.

**Summary**

The proposed associations (of periodontal infections as risk factors for systemic disease) appear to be biologically plausible, but at this stage it is not possible to draw the magnitude of their biological effects. Nevertheless, studies underscore that the oral cavity is an integral part of the human body, and that systemic health must encompass oral, and periodontal, health as well.