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Gingivitis as a risk factor in periodontal disease

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Abstract

Background: Dental plaque has been proven to initiate and promote gingival inflammation. Histologically, various stages of gingivitis may be characterized prior to progression of a lesion to periodontitis. Clinically, gingivitis is well recognized.

Material & Methods: Longitudinal studies on a patient cohort of 565 middle class Norwegian males have been performed over a 26-year period to reveal the natural history of initial periodontitis in dental-minded subjects between 16 and 34 years of age at the beginning of the study.

Results: Sites with consistent bleeding (GI = 2) had 70% more attachment loss than sites that were consistenly non-inflamed (GI = 0). Teeth with sites that were consistently non-inflamed had a 50-year survival rate of 99.5%, while teeth with consistently inflamed gingivae yielded a 50-year survival rate of 63.4%.

Conclusion: Based on this longitudinal study on the natural history of periodontitis in a dentally well-maintained male population it can be concluded that persistent gingivitis represents a risk factor for periodontal attachment loss and for tooth loss.

Dedication:
This manuscript is dedicated to the memory of our co-author, Harald Löe, friend, colleague and mentor, who died on 9 August 2008 during the preparation of this paper. Harald's foresight in carrying out the surveys on the natural history of periodontal disease made it possible to answer the pertinent questions on the significant role of gingivitis in periodontitis progression and tooth loss. Originally, he was scheduled to present this paper at the FDI Congress in Stockholm in September 2008.

Key words: epidemiology; gingivitis; periodontitis progression; prevention; risk factor; tooth loss

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We are here in Stockholm this week to celebrate the 100th Anniversary of the Swedish Dental Association and to congratulate our Swedish colleagues on their many important contributions to the science and practice of dental medicine.

Let us be reminded, however, that during the first 50 years of the Association's history, insufficient knowledge existed regarding the nature and causes of periodontal disease, and there was little agreement on their clinical management both in Sweden and worldwide.

It was from this state of ignorance and professional inaction that the Scandinavian school, led by Dr. Jens Wærhaug during the early 1950s, initiated what would amount to a revolution in periodontal research and practice.

Conflict of interest and source of funding statement

The symposium ''Inflammation: is it a threat to your patients'' was presented at the FDI World Dental Congress in Stockholm Sweden in September 2008 and funded by Johnson & Johnson. The authors received a speaking engagement fee and a fee for the preparation of this manuscript from Johnson & Johnson Ltd. The studies have been partially funded by the Clinical Research Foundation (CRF) for the Promotion of Oral Health, Brienz, BE, Switzerland.

Dental Plaque

First microscopic and electron microscopic research revealed the intimate relationship between dental plaque and the gingival and periodontal tissues.

Then, epidemiological studies in many countries pointed to a close association between tooth deposits and periodontal diseases.

Finally, in 1965, the experimental gingivitis studies demonstrated that the accumulation of plaque on healthy gingiva produced gingivitis (Löe et al. 1965) (Fig. 1a–d), and that after reinstitution of oral hygiene measures for 7 days, the gingiva reverted back to normal (Fig. 2). These studies also described the sequential development of gingival plaque from a simple monolayer of Gram-positive coccoid bacteria colonizing the enamel surface and the marginal gingiva to a complex microbial plaque dominated by Gram-negative anaerobic cocci, filaments and spirochetes (Theilade et al. 1966). These and other studies came to be the ultimate documentation that bacterial plaque was something very different from food debris, something much more colourful than *Materia Alba*, and much more interesting than just ''Schmutz'' (Fig. 3a and b). Consequently, the research to understand more fully the interaction between the infectious agents and the lost tissues in the transition from health to disease, and in the progression from gingivitis to periodontitis was intensified.

Supragingival plaque related to healthy gingival tissues has a bacterial com-

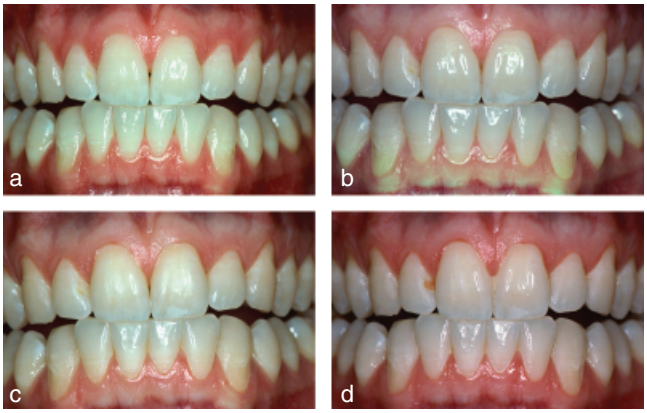

Fig. 1. Experimental gingivitis in humans (Löe et al. 1965): (a) Clinically plaque- and inflammation-free dentition of an experimental subject on Day 0. (b) Same subject after 7 days of abolished oral hygiene. (c) Two weeks of abolished oral hygiene results in localized early signs of gingivitis (tooth 11). (d) Same subject at the end of a 3-week period of nooralhygiene. Plaque accumulation resulted in the development of a generalized gingivitis.

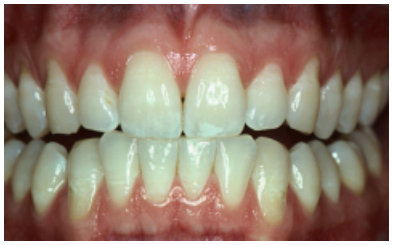

Fig. 2. Experimental gingivitis in humans (Löe et al. 1965). Same subject as in Fig. 1, but after 10 days of re-instituted oral hygiene practices. Plaque removal resulted in the resolution of inflammation. Clinically perfect gingival conditions.

position that is different from that of plaque associated with gingivitis, which again is different from the make-up of subgingival plaque of the progressing or advanced periodontal lesion.

Perhaps >300 different types of microorganism have been found in well-developed human dental plaque, some of which have been identified, and others have not been identified. Some may be important in the pathogenesis of the disease, and others may not. Research, so far, suggests that it is not one or two organisms that are responsible for periodontal pathology, but several. Today, there is a relative agreement among authorities that at least seven to eight organisms are fairly certain to be involved in various types of periodontal disease. These are:

Aggregatibacter actimomycetemcomitans,
Porphyromonas gingivalis,
Tannerella forsythia,
Prevotella intermedia,
Campylobacter rectus,
Spitochetes.

Those and possibly other not yet identified organisms are considered to be important in gingivitis development, in progression from gingivitis to periodontitis, as well as in the advancing lesion of both chronic and aggressive periodontitis.

The fact that seven to eight organisms in varying combinations may relate to the various aspects of the disease can hardly satisfy the criteria for the so-called ''specific plaque hypothesis'', and some may be on the side of those who speak in favour of the ''non-specific plaque hypothesis''. The least that can be said about the specificity of the periodontal infection is that the Gram-negative, anaerobic microbiota continues to be prominent both in gingivitis development and in the advancing or advanced periodontal lesion. The spirochetes are persistently interesting, but, because culturing has been difficult, they have not regularly been part of the protocols. Finally, perhaps mention should also be made of the suggestion that development of human aggressive periodontitis has been associated with combinations of herpes viruses and putative periodontopathic bacteria.

Over the past few years, a new word has found its way into the discussion for what people understand as dental bacterial plaque. The catchword is ''biofilm''. After periodontal research has used more that 100 years since Dr. Black first introduced the term dental plaque to subject this material to scientific scrutiny, plaque is now reasonably well described and widely understood. However, new aspects of the life within the bacterial community with its structures of communication as well as the phenomenon of quorum sensing justify this new term as an expression of our more detailed understanding of the biofilm.

Histopathology

In most cases, initial plaque development starts in the niche created where the gingival margin meets the tooth surface (Fig. 4). In these cases, the bacterial plaque is located adjacent to the non-keratinized crevice epithelium, and the bacteria would have to exert their effect from this juxta position. In other instances, the microorganisms seem to invade the tissues. In either case, tissue destruction will occur as a direct result of microbial action through their release of toxins, lipopolysaccharides or enzymes, or indirectly, as a result of activation of the patient's cellular and bacterial inflammatory systems – the so-called host responses, which may serve to both damage and protect the periodontal tissues.

Although no one has directly observed the earliest stages of gingivitis development, it is surmised that these include processes germane to acute inflammation:

- transudation of serum through the vascular endothelium,
- extravasation of leucocytes and their outward emigration,
- widening of the intercellular spaces of the surface epithelia and
- gradual release of immuno-inflammatory mediators with a variety of potentials, such as cytokines [interleukin (IL)-1α, ILβ, IL-6, IL-8 and tumour necrosis factor-α].

These and others have proven their effects on signalling gene expression, mobilizing of inflammatory cells in mediating the release of enzymes like collagenases, other proteolytic enzymes, including the metallo-proteinases, which are responsible for the degradation, and the extracellular matrix of the connective tissue. Also, these in turn give rise to potent products, such as prostaglandins, particularly PGE_2 and others that are involved in several inflammatory

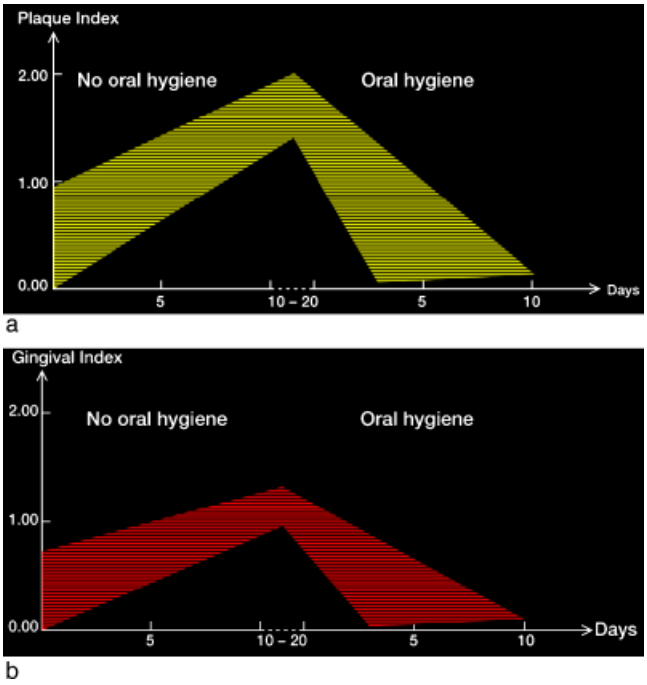

Fig. 3. Experimental gingivitis in humans (Löe et al. 1965). Graphs demonstrating the cause-and-effect relationship between dental plaque and the development of gingivitis (b). As the Plaque indices increase (a), the gingival indices follow, yielding the host response to the bacterial challenge (b). Following re-institution of oral hygiene (a), gingival health is, again, reached within a week to 10 days (b).

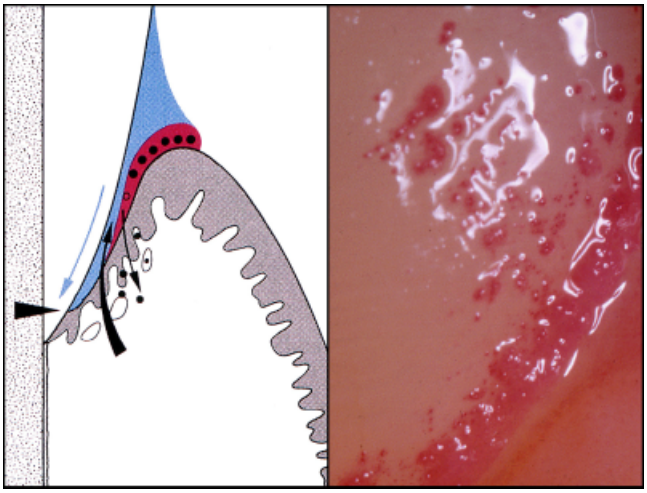

Fig. 4. Plaque begins to form in the gingival sulcus and other protected niches of the tooth. (a) Destruction of collagen will occur as a direct result of microbial action through their release of toxins, lipopolysaccharides or enzymes. (b) Bacterial plaque forms as a biofilm in the gingival sulcus shortly after the cleansing of the tooth surface. Three-day-old plaque.

processes during the progression of the disease, of which bone resorption might be the most important.

Also during the early stages of the process, various bacterial antigens will elicit the production of antibodies, mobilize the complement system and release other immunoglobulins, along with the emergence of phagocytic cells such as plasma cells and activation of other cell types such as lymphocytes and macrophages (Fig. 5a and b). As these complex processes pervade the marginal gingiva, the developing gingival lesion matures into chronic gingivitis, with massive accumulations of cells and fluid overtaking the connective tissues stroma.

Clinical Gingivitis

The earliest clinical sign of gingival inflammation is the *transudation of gingival fluid*. This thin and almost a cellular transudate is gradually supersceded by a fluid consisting of serum plus leucocytes.

The *redness* of the gingival margin arises partly from the *aggregation and enlargement of blood vessels* in the immediate subepithelial connective tissue and the loss of keratinization of the facial aspects of gingiva (Fig. 6a and b).

Swelling and loss of texture of the free gingiva reflect the loss of fibrous connective tissue and the semi liquidity of the interfibrillar substance.

Individually and collectively, the clinical symptoms of chronic gingivitis are rather vague, and usually *painless*. These features leave most patients unaware of the disease and are generally underestimated by the dental practitioners. Chronic gingivitis rarely shows spontaneous *bleeding*. The fact that the gingival tissues can be provoked to bleed just by touching the gingival margin with a blunt instrument (Fig. 7) [as during tooth brushing or in assessing the gingival index (GI)] suggests that the epithelial changes and the vascular transfigurments are quite conspicuous.

Progression to Periodontitis

Cross-sectional epidemiological studies from many countries have indicated that gingivitis is common both in primary and in secondary dentitions of children, and affects most adults. National probability surveys in some industrialized countries have found that gingivitis occurs in the majority of teenagers and adults, but that only a few, perhaps $< 10\%$ of the total gingival sites, ''bleed on probing'' (GI = 2). Similar data based on probability samples are not available for developing regions, but it has been suggested that gingivitis might be highly prevalent, extensive and severe.

The distribution of gingivitis in any population is important since current theory holds that the gingival lesion is the precursor of periodontitis. Clearly, not all gingivitis lesions progress to periodontitis. Actually, the proportion of gingival lesions converting to periodontitis, and the factor causing this conversion have not been well understood. Most seem to think, however, that the established periodontitis lesion was preceded by gingivitis.

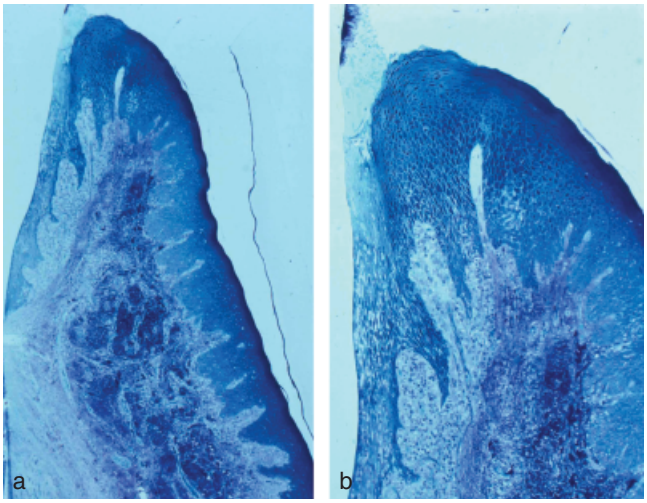

Fig. 5. (a) Photomicrograph of a gingivitis lesion. The inflammatory infiltrate is clearly visible: extravasations of leucocytes and their outward emigration, widening of the intercellular spaces of the surface epithelia and a gradual release of immuno-inflammatory mediators with a variety of potentials. (b) Higher magnification of (a): Bacterial plaque is located adjacent to the non-keratinized crevice epithelium. Emergence of phagocytic cells such as plasma cells and activation of other cell types such as lymphocytes and macrophages.

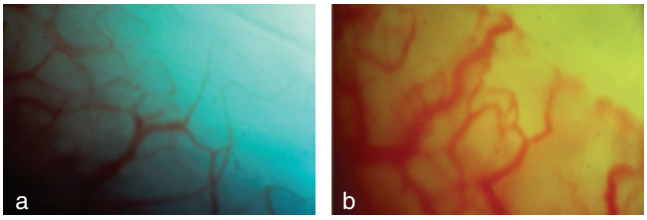

Fig. 6. Aggregation and enlargement of blood vessels in the immediate subepithetial connective tissue. (a) Vital microscopy of a clinically healthy gingival margin. Presence of numerous fine capillary networks. (b) Vital microscopy of a gingival margin presenting with gingivitis. Capillary loops are enlarged. Clinically, these changes are recognized as redness and swelling of the gingival margin.

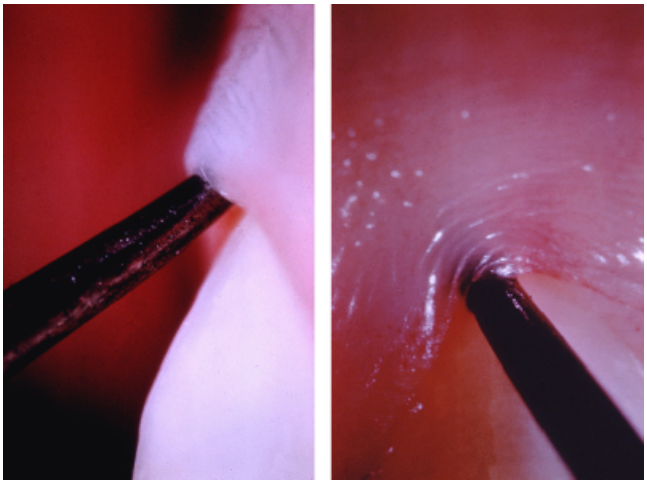

Fig. 7. In health, the insertion of a blunt instrument or probe into the gingival crevice will maintain its integrity. However, bleeding may be induced as a result of developing gingivitis.

While traditional cross-sectional human surveys may describe reasonably well the distribution of disease and the associated factors, cross-sectional studies are unable to characterize the continuous process and the temporal and spatial relationships between the various factors influencing the initiation and the progression of the disease. Also, the determination of the cause of a disease or the definition of the true risk factors of a disease requires a longitudinal design of a study.

Longitudinal Studies

The material presented in this review is obtained from longitudinal studies of periodontal disease in humans (Heitz-Mayfield et al. 2003, Schätzle et al. 2003a, b, 2004).

The cohort was established in Oslo Norway in 1969, and consisted of 565 randomized healthy, well-educated males between 16 and 34 years old. All participants were born in Oslo, and all had been enrolled in the City Dental Program during childhood, and reported to have subsequently seen their private dentist on a regular basis, as well as performing daily oral hygiene care.

Subsequent clinical examination of the participants occurred in 1971, 1973, 1975, 1981, 1988 and 1995. As in most longitudinal investigations of this size and length, a certain member of the participants dropped out, and could not be followedup. Others would miss one or more examinations, but might show up for the last survey; 223 men showed up for the last examination covering the entire age range from 16 to 60 years.

The following clinical indices were collected during the 26-year observation period: plaque index, GI, calculus index, caries index, gingival recession and loss of attachment. (Pocket depths were derived from calculating LA and GRI.)

These studies have shown that in well-educated middle-class men who had received state-of-the-art professional and personal dental care during childhood, adolescence and adulthood, the dentition is maintained in health and function throughout life. The 16-year-old boys had 27.4 teeth (excluding wisdom teeth), and as the men approached 60 years, they still had 27.1 teeth. They have lost 0.3 teeth in 45 years of adult

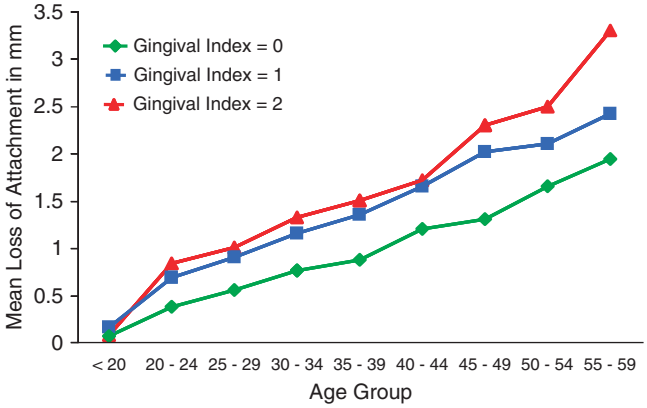

Fig. 8. Effect of different gingivitis levels on the loss of attachment. The development of periodontitis only occurs in areas of long-standing gingivitis (from: Schätzle et al. 2003a).

life, and the mortality rate was 0.01 teeth/year (Schätzle et al. 2004)

Although none of the participants at any one survey exhibited a dentition completely free of plaque, it is noteworthy that approximately 60–70% of the total tooth surfaces were either plaque free or scored Pl $I = 1$ (invisible plaque), and that throughout the age range (16–60 years) only 20–30% of the surfaces scored Pl $I = 2$ (visible plaque).

Gingival indices also varied very little during adult life and ranged between GI = 0.1 and 0.9. In other words, the gingival health of this group of people must be characterized as good to excellent, and the frequency of GI = 2 scores (bleeding on probing) occurred only in 10–20% of sites in all men 16–60 years of age (Schätzle et al. 2003a).

Attachment loss occurred in a few sites already at 16 years, but mainly as gingival recession on buccal surfaces (Heitz-Mayfield et al. 2003). Deepened pockets were scarce below 40 years of age, and rarely exceeded 3.4 mm in depth. The mean individual loss of attachment (LA) and the frequency of sites with attachment loss increased somewhat during the 40s and 50s, and reached a maximum (LA = 2.44 mm) as the men approached 60 years. However, <0.5% of the sites had lost >4 mm.

To analyse *the role of gingival inflammation* in the pathogenesis of the periodontal lesion, three gingival index severity groups were established across all age groups according to their degree of clinical inflammation scores over the 26-year observation period (Schätzle et al. 2003a).

The results show that gingival units that consistently scored GI = 0 experienced a mean cumulative LA over the 60 years life span of <2 mm (range 0.08–1.94). This attachment loss essentially occurred in buccal sites of young men below 40 years, displaying gingival recession. Sites with slight inflammation (GI = 1) showed a cumulative attachment loss of >2 mm (range 0.17–2.42), and in sites that consistently bleed on probing (GI = 2), the mean LA was >3 mm (range 0.04–3.53) (Schätzle et al. 2003a) (Fig. 8).

From the age of 40 and 50 years, pocket formation increased in extent and depth in sites exhibiting gingival inflammation. As the men approached 60 years of age, gingival sites that, throughout the observation period consistently bleed on probing, had 70% more attachment loss than sites that consistently were non-inflamed, yielding an odds ratio of 3.22 for inflamed sites converting to attachment loss. Also, subgingival calculus formation increased the odds ratio for converting to attachment loss to 4.22, for the GI = 2 group, compared with sites of the GI = 0 cohort (Schätzle et al. 2003a).

From this part of the analysis, it was concluded that it has now convincingly been demonstrated that the *development of periodontitis only occurs in areas of long-standing gingivitis*.

In order to further elucidate the transition from gingivitis to peridoontitis, the *incidence of the initial loss of attachment* over the 60-year life span was next assessed (Heitz-Mayfield et al. 2003). The loss of the first 2 mm or more of periodontal attachment as measured apically from the cemento-enamel junction was termed as initial loss of attachment (ILA). The incidence of ILA was established for all age levels, all teeth and groups of teeth as well as for the type of lesion expressed (gingival recession, pockets alone or in combination with recession). Again, and not surprisingly, at age 20 years and before ILA occurred in a few buccal sites in a few individual and almost all were gingival recessions.

At 40 years of age, still <10% of the sites with ILA showed either pocket formation or condensation of attachment loss and pocketing. As the men aged 50, 55, 60 years, however, approximately 30%–50% of the sites had ILA (Heitz-Mayfield et al. 2003).

It appears then that the incidence of attachment loss of ⩾2 mm expressed as deepening of the periodontal pocket is absent or extremely low during the early years of life. In fact, gingival recession was the dominant type of initial attachment loss during the first 40 years of life. Pocket formation starts earliest around 50 years of age, and increases in incidence towards the age of 60.

Another analysis of this unique cohort aimed at the assessment of the long-term influence of gingival inflammation on tooth survival (Schätzle et al. 2004).

For tooth-specific calculations, three gingival index groups reflecting their history of inflammation over the 26 years were established. For this reason, the minimal and maximal GI value over all sites was determined:

- Severity I: teeth consistently scoring a minimum of GI = 0 and a maximum of GI⩽1 in all sites.
- Severity II: teeth in which all sites always scored a minimum of GI = 1 and a maximum of GI⩽2.
- Severity III: teeth that always scored a minimum of GI = 2 (bleeding on probing) in all sites and at all observations.

All other teeth not fulfilling these criteria were not considered for further evaluation.

Four hundred and eighty-seven patients with 13,285 teeth in 1969 were followed up for at least two surveys. Of the 487 subjects, 412 (85%) had lost no teeth and the remaining 75 of the re-examined individuals accounted for the 126 teeth lost.

The Kaplan–Meier cumulative survival distribution (Fig. 9) for the three defined GI Severity Groups showed

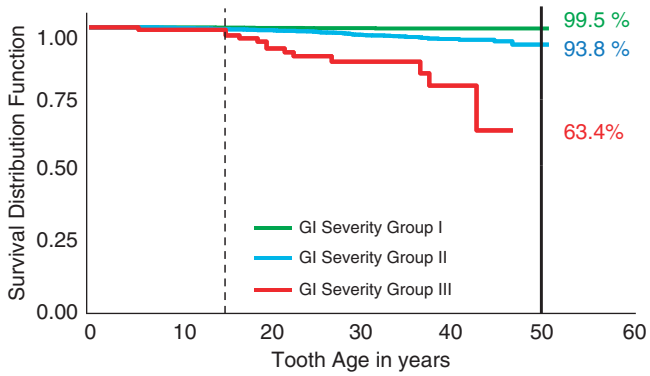

Fig. 9. Effect of different gingivitis levels on tooth loss. Survival distribution function for different gingival index Severity Groups. After 50 years of tooth age, the cumulative survival for teeth with healthy gingival tissues is 99.5%. Teeth with always bleeding gingivae demonstrate a cumulative survival of 63.4% after 48 years of tooth age (from: Schätzle et al. 2004).

that before a tooth age of approximately 15 years, tooth loss was extremely rare. After a tooth age of 20 years, GI Severity Group III yielded a significantly increased cumulative tooth loss when compared with both GI Severity Groups II and I.

It is remarkable to note that GI Severity Group I, where no bleeding on probing was ever scored throughout the observation period, yielded a cumulative tooth survival of 99.5% at a tooth age of *51 years*. This suggests that *clinically healthy gingiva is a prognostic indicator of tooth longevity*.

The fact that the GI Severity Group II demonstrated a cumulative tooth survival rate of 94% after 51 years of tooth age supports the concept that occasionally, bleeding tooth sites provide a much smaller risk for tooth loss than regularly bleeding gingivae.

The risk of losing a tooth showed a wide range of odds ratios. Teeth always surrounded by healthy or slightly inflamed gingiva had an 8.4 times lower risk of being lost as compared with teeth surrounded by an inflamed gingiva that occasionally bled on probing, and a 45.8 times lower risk than teeth that were always surrounded by an inflamed gingiva that bled on probing. Teeth with slightly inflamed gingiva had a 5.4 times lower risk of tooth loss than those that showed bleeding on probing.

This study has clearly established that gingival inflammation was a risk factor for tooth loss. Teeth consistently surrounded by inflamed gingiva at all surveys during the 26-year observation period had a significantly higher risk of being lost than teeth with no or only slight inflammation.

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Clinical Relevance

Scientific rationale for the study: Gingivitis may be perceived as a protective host response against the bacterial challenge. It is unclear wether or not gingivitis may lead to detrimental effects.

Principal findings: Teeth with consistently inflamed dentogingival units showed over a 26-year observation period greater attachment loss and a higher chance for tooth loss than teeth with consistently non-inflamed dentogingival units.

Practical implications: Inflammation of the gingival tissues represents not only the precursor of periodontitis but also a clinically relevant risk factor for disease progression and tooth loss.