



# Endpoints of active periodontal therapy

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## Abstract

**Aim:** Position paper on endpoints of active periodontal therapy for designing treatment guidelines. The question was as follows: How are, for an individual patient, commonly applied periodontal probing measures—recorded after active periodontal therapy—related to (a) stability of clinical attachment level, (b) tooth survival, (c) need for re-treatment or (d) oral health-related quality of life.

**Methods:** A literature search was conducted in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to 07 June 2019>.

**Results:** A total of 94 papers were retrieved. From the literature search, it was found that periodontitis patients with a low proportion of deep residual pockets after active periodontal therapy are more likely to have stability of clinical attachment level over a follow-up time of  $\geq 1$  year. Other supporting literature confirms this finding and additionally reports, at the patient level, that probing pocket depths  $\geq 6$  mm and bleeding on probing scores  $\geq 30\%$  are risks for tooth loss. There is lack of evidence that periodontal probing measures after completion of active periodontal treatment are tangible to the patient.

**Conclusions:** Based on literature and biological plausibility, it is reasonable to state that periodontitis patients with a low proportion of residual periodontal pockets and little inflammation are more likely to have stability of clinical attachment levels and less tooth loss over time. Guidelines for periodontal therapy should take into consideration (a) long-term tangible patient outcomes, (b) that shallow pockets ( $\leq 4$  mm) without bleeding on probing in patients with  $<30\%$  bleeding sites are the best guarantee for the patient for stability of his/her periodontal attachment, (c) patient heterogeneity and patient changes in immune response over time, and (d) that treatment strategies include lifestyle changes of the patient. Long-term large population-based and practice-based studies on the efficacy of periodontal therapies including both clinical and patient-reported outcomes (PROs) need to be initiated, which include the understanding that periodontitis is a complex disease with variation of inflammatory responses due to environment, (epi)genetics, lifestyle and ageing. Involving people living with periodontitis as co-researchers in the design of these studies would also help to improve their relevance.

## KEYWORDS

endpoint, oral health-related quality of life, patient-reported outcomes (pros), periodontitis, tooth survival

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## 1 | INTRODUCTION

Active periodontal therapy has always been provided to periodontitis patients to establish conditions which allow the patient to maintain a dentition without further breakdown of the periodontium, that is (a) to prevent further episodes of periodontitis, (b) to reduce and even eliminate gingival inflammation, (c) to reduce and even eliminate deepened pockets and (d) to regain periodontal attachment of the tooth; thus ultimately to prevent tooth loss and loss of dental functions (Pihlstrom, 1992). Active periodontal therapy is defined as a standard treatment consisting of oral hygiene instructions, biofilm and calculus removal (a.k.a. initial or cause-related therapy) with or without adjunctive antimicrobials and with or without surgical treatment. In fact, periodontal therapies should be directed at tangible benefits to the patient such as maintenance or enhanced quality of life, chewing comfort, aesthetics and decreased tooth mortality (Hujoel & DeRouen, 1995) as well as reducing negative effects on general health. It has been suggested that loss of teeth may also result in the consumption of an unhealthy diet, richer in unhealthy fatty acids and carbohydrates and containing reduced amounts of dietary fibres (Chauncey, Muench, Kapur, & Wayler, 1984; Zhu & Hollis, 2014), the latter being risk factors for obesity, diabetes and cardiovascular diseases. A healthy and well-functioning dentition is as much part of a healthy body as any other vital organ.

Delphi survey panels consisting of periodontists have proposed that the absence of pain, acceptable aesthetics and patient satisfaction are extremely important outcomes for successful periodontal treatment (Lightfoot, Hefti, & Mariotti, 2005a, 2005b). A recent study amongst 14,620 patients in 233 non-specialist dental practices across the UK found the patient-reported outcomes (PROs) oral pain/discomfort, dietary restrictions and dental appearance to be positively associated with worse periodontal health represented by increased pocket depths, more alveolar bone loss and more bleeding on probing (Sharma, Yonel, Busby, Chapple, & Dietrich, 2018). Previously it was reviewed that there is a weak relationship between the oral health condition measured by dental professionals and oral health judged by patients (Öhrn & Jönsson, 2012), confirming that perceived oral health by dental patients is not captured in the traditional clinical examinations (Aslund, Pjetursson, & Lang, 2008; Buhlin, Gustafsson, Andersson, Hakansson, & Klinge, 2002). Therefore, clinicians and researchers should also include endpoints to measure periodontal treatment outcomes that are relevant to patient perception and priorities, including their overall systemic health (Needleman, McGrath, Floyd, & Biddle, 2004).

Shallow residual periodontal pockets are considered to be unfavourable ecological niches for a dysbiotic biofilm. This concept has been brought forward repeatedly in various reviews and opinion papers (Bartold & Van Dyke, 2019; Kilian et al., 2016; Loos & Van Dyke, 2020; Marsh, 1994; Marsh & Zaura, 2017). Therefore, it has been argued that all periodontal treatment procedures for periodontitis should aim to achieve low levels of bleeding on probing (e.g.,  $\leq 15\%$  of sites), shallow probing pocket depths ( $\leq 4$  mm) and absence of suppuration (Sanz et al., 2015; Tonetti et al., 2017).

### Clinical Relevance

*Scientific rationale for the study:* To investigate what we know about tangible patient outcomes after active periodontal therapy and to make recommendations for practice and research.

*Principal findings:* Traditional periodontal probing measures are considered surrogate endpoints and are not tangible to the patient. Periodontitis patients with a low proportion of residual periodontal pockets and little inflammation are more likely to have stability of clinical attachment levels and less tooth loss over time.

*Practical implications:* Active periodontal treatment should aim for shallow non-bleeding periodontal pockets and tangible patient-reported outcomes.

However, it is unclear what constitutes tangible treatment outcomes for the patients.

The aim of the present position paper was to answer the following questions: How are, for an individual patient, commonly applied periodontal probing measures—recorded after active therapy—related to (a) stability of clinical attachment level, (b) tooth survival, (c) need for re-treatment or (d) oral health-related quality of life? With this, it was the intent to create awareness and to add issues for plenary discussions on the definition and meaning of PROs of active periodontal therapy, for the dental researchers engaged in designing clinical periodontal treatment guidelines.

## 2 | METHODS

This review is limited to the most widely used periodontal probing measures, and therefore, the use of dental radiographs, microbiological and other biological or biochemical measures is not included. Since the value of periodontal probing measures as endpoints of active periodontal therapy is unclear, we have explored their relationship with the following long-term clinical and PROs:

1. Stability of clinical attachment level.
2. Tooth survival.
3. Need for re-treatment.
4. Oral health-related quality of life.

To investigate these relationships, we considered the following selected clinical probing measures at the end of active periodontal treatment (any type of treatment of periodontitis including non-surgical [with or without adjuncts] and surgical therapy):

- The extent of shallow pockets (probing depth  $\leq 4$  mm)
- Residual probing depth ( $\geq 5$  mm)
- Change in probing depth

**TABLE 1** The strategy of a literature search conducted in Ovid MEDLINE(R) and Epub ahead of print, In-Process & Other Non-Indexed Citations and Daily <1946 to 07 June 2019>

1	*Clinical trials as topic/
2	"Outcome assessment (Health Care)"/st, mt [Standards, Methods]
3	*Longitudinal studies/
4	Dental research/mt [Methods]
5	*Terminology as topic/
6	*Research design/
7	1 or 2 or 3 or 4 or 5 or 6
8	*Periodontal index/
9	Periodontitis/th [Therapy]
10	Periodontal attachment loss/di, th [Diagnosis, Therapy]
11	Periodontics/st [Standards]
12	Tooth loss/pc [Prevention & Control, Diagnosis]
13	Periodontal diseases/th [Therapy]
14	8 or 9 or 10 or 11 or 12 or 13
15	7 and 14

Note: In our literature search (total 94 papers), we found the following type and numbers of papers: three study protocols, three letters to the editor, four opinion papers, one systematic review, nine narrative reviews, 53 discussion papers on methodological issues, two reports on Delphi panel surveys, five commentaries, three guidelines, one experimental modelling study and 10 clinical studies. The full search results are accessible as Appendix S1 on line.

- Change in clinical attachment level
- Bleeding on probing

The search strategy is provided in Table 1 and the literature search yielded 94 papers, mainly on methodological and study design issues (list of titles and abstracts is provided in the Appendix S1 available online). We focused specifically on issues and reports at the patient level, as it is the patient who may develop recurrent periodontitis and who has the need to seek re-treatment, who may experience tooth loss during the periodontal maintenance phase and who judges his/her own oral health-related quality of life (Hujoel, 2004; Needleman et al., 2004; Öhrn & Jönsson, 2012). However, since potentially eligible studies addressed a range of research questions, designing a comprehensive search was challenging. Therefore, we supplemented the electronic search with studies retrieved from reference lists. Moreover, we stratified data into shorter-term (3–12-month follow-up) and longer-term studies ( $\geq 12$  months).

### 3 | RESULTS

#### 3.1 | Endpoints defined

Patients, policymakers and insurance companies may have different perceptions of pursued endpoints of periodontal therapy than

clinicians and periodontal researchers. An endpoint is an event or outcome that can be measured objectively to determine whether an intervention being studied is beneficial (Hujoel & DeRouen, 1995). In this context, we might differentiate between true and surrogate endpoints of treatment (Hujoel & DeRouen, 1995). Surrogate endpoints, which include probing pocket depth reduction and gain in clinical attachment level, may not provide unambiguous evidence that a certain treatment yields concrete patient benefits. Nevertheless, few experimental (as opposed to observational) periodontal treatment studies have investigated true endpoints such as tooth retention, perhaps because of the duration of follow-up required to make this outcome meaningful to measure. Another true outcome, quality of life, has been included although the number of trials reporting this measure is low and it is not clear how responsive such tools are to assess treatment response as compared to their original application, which was in cross-sectional epidemiological studies. There are a large number of surrogate endpoints used in periodontal treatment studies, and these have been tabulated (Table 2) based on a survey of endpoint characteristics in periodontal trials (Hujoel & DeRouen, 1995). The latter authors conclude that for example clinical attachment level is a weak predictor of tooth loss because it cannot capture a substantial proportion of the effect of treatment on tooth mortality. Nevertheless, loss of clinical attachment level was informative for later tooth loss in a Norwegian population (Hujoel, Loe, Anerud, Boysen, & Leroux, 1999).

#### 3.2 | Findings on the defined endpoints

##### 3.2.1 | Stability of clinical attachment level

We found only one systematic review to investigate residual probing depth and bleeding on probing following initial periodontal therapy to evaluate the stability of clinical attachment level over time (Renvert & Persson, 2002). In that review, only publications on chronic or adult forms of periodontitis were eligible for inclusion, excluding aggressive periodontitis. Data were presented at the patient rather than the site level. Loss of clinical attachment level was defined as  $\geq 1.5$  mm compared to 3-month post-treatment data by linear regression analysis or as  $\geq 2$  mm between baseline and study endpoint measurement. The systematic review yielded only one study (Claffey & Egelberg, 1995) out of 47 potentially eligible. There were no short-term studies (3–12-month follow-up). The reviewers report from the Claffey and Egelberg (1995) study a significant inverse correlation between the stability of clinical attachment level over follow-up time and the patient-mean proportion of sites having residual probing depths  $\geq 6$  mm at the 3-month time point after active periodontal therapy. Thus, periodontitis patients with a low proportion of deep residual pockets after initial therapy are more likely to have stability of clinical attachment level over a follow-up time of  $\geq 12$  months (Renvert & Persson, 2002). In contrast, the parameter bleeding on probing in the original study (Claffey & Egelberg, 1995) did not show a significant association with stability of clinical attachment level (Renvert & Persson, 2002).

**TABLE 2** Listings of true and surrogate endpoints of periodontal therapy to consider when evaluating the success of periodontal therapy

True endpoints	Surrogate endpoints <sup>a</sup>			
	Anatomical landmarks using non-surgical technologies	Anatomical landmarks using surgical technologies	Inflammation, plaque and other miscellaneous measures	Microbiology
Tooth loss	Clinical attachment level	Histology measurements <sup>c</sup>	Bleeding	Microscopy
Pain	Probing pocket depth	Re-entry surgery measurements	Suppuration	Culture
Chewing ability	Furcation assessment		Gingival crevicular fluid	DNA-probes
Aesthetics	Recession		Plaque	Microbiome
Oral health-related QoL	Radiography Composite measures <sup>b</sup>		Miscellaneous <sup>d</sup>	

Note: DNA-probes, measurements on deoxyribonucleic acid originating from specific target bacterial species.

Abbreviation: QoL, Quality of Life.

<sup>a</sup>According to a review (Hujuel & DeRouen, 1995).

<sup>b</sup>For example % subjects losing  $\geq 3$  mm in clinical attachment level or experiencing a periodontal abscess or % subjects with no inflamed sites  $\geq 5$  mm.

<sup>c</sup>Histological sections or analyses on extracted teeth.

<sup>d</sup>For example tooth mobility and certain cell counts.

A more recent landmark paper concluded essentially the same as above: based on the long-term follow-up of 172 patients in periodontal maintenance therapy, it was found that the presence of deep ( $\geq 6$  mm) residual pockets was a risk factor for patients to have further periodontal disease progression (Matuliene et al., 2008).

### 3.2.2 | Tooth survival

The above referred systematic review (Renvert & Persson, 2002) used residual probing depth and bleeding on probing also as parameters to evaluate tooth survival over time, but failed to find any papers.

Several studies were found from reference lists and not from our search, which on the first view might inform on this topic, for example (Chambrone, Chambrone, Lima, & Chambrone, 2010; Faggion, Petersilka, Lange, Gerss, & Flemmig, 2007; Martinez-Canut, 2015; Martinez-Canut et al., 2018). However, these important studies investigated prognostic factors of initial periodontal status (i.e., at baseline, prior to treatment) and this is different from the focus of the current review which was to determine the effect of treatment outcomes on future tooth loss. These studies were therefore unable to offer additional data to this position paper. Thus, with the current approach, it can be concluded that there is both a limited amount of data in the literature and considerable heterogeneity.

Nevertheless, Matuliene and co-workers identified that *after active periodontal therapy*, residual pockets  $\geq 6$  mm and full-mouth bleeding scores of  $\geq 30\%$ , represented a risk for tooth loss for the patient (Matuliene et al., 2008). However, in a multivariate regression analysis for tooth loss in the maintenance phase, statistically significant clinical outcomes at the patient level were full-mouth bleeding scores  $\geq 30\%$ , baseline disease classification and numbers of years of maintenance therapy; whilst residual periodontal pocket depth was important, the number of residual periodontal

pockets  $\geq 5$  mm was not significantly associated with risk of tooth loss and the number of residual periodontal pockets  $\geq 6$  mm was close to significantly predictive ( $p = .053$ ; Matuliene et al., 2008). Applying the periodontal risk assessment model (Lang & Tonetti, 2003), the number of residual pockets of  $\geq 5$  mm failed to be a patient factor predicting tooth loss in the maintenance phase (Matuliene et al., 2010). In yet another analysis of the same sample, the odds of loss of multirrooted teeth were more than three times when residual periodontal pocket depth  $\geq 6$  mm was present compared to  $< 6$  mm ( $p = .0007$ ; Salvi et al., 2014).

### 3.2.3 | Need for re-treatment

In our search, neither short-term studies (3–12-month follow-up) nor longer-term studies ( $\geq 12$  months follow-up) appeared investigating the use of various probing measurements on the need for periodontitis re-treatment.

Notably, if one equates “progression of periodontitis” with the need for re-treatment, again from the Matuliene papers et al., indicative observations can be retrieved. From a standard multivariable logistic regression analysis, having at least one site with a residual probing depth of  $\geq 6$  mm, amongst other patient factors, remained a statistically significant risk factor for disease progression (Matuliene et al., 2008). However, no clinical probing measures at the end of active periodontal treatment were found to contribute significantly to the risk of recurrence of periodontitis (presumably “need for re-treatment”) when applying the periodontal risk assessment model (Matuliene et al., 2010).

### 3.2.4 | Oral health-related quality of life

In our search, neither short-term studies (3–12-month follow-up) nor longer-term studies ( $\geq 12$  months follow-up) appeared investigating

the use of various probing measurements on the oral health-related or general quality of life.

## 4 | DISCUSSION AND CONSIDERATIONS WHEN DEVELOPING PERIODONTAL THERAPY GUIDELINES

### 4.1 | Discussion on the aim of review and main findings

In this position paper, we discuss endpoints at the patient level of active periodontal therapy to be considered when dental researchers and clinicians design periodontal treatment guidelines. How are for an individual patient after active periodontal therapy (a) stability of clinical attachment level, (b) tooth survival, (c) need for re-treatment or (d) oral health-related quality of life, related to commonly and easily applied periodontal probing measures, that is generalized pocket closure (probing depths  $\leq 4$  mm), a certain patient level of residual pockets (e.g., residual probing depths  $\geq 5$  mm), a given level of accumulated changes in probing depth and in clinical attachment level, and a patient-based value for number or proportion of sites showing bleeding on probing. In essence, although the literature is abundant on the plain presentation of probing measures in numerous clinical studies on the site level, tooth level and type of tooth with or without severe furcation problems, surprisingly, virtually absent are reports that use these commonly applied periodontal probing measures (pockets  $\leq 4$  mm, residual probing depth, change in probing depth, change in clinical attachment level or bleeding on probing) *after* completion of the active periodontal treatment, subsequently to be used as new baseline measures for the study of the four patient endpoints considered in this review. Of these, tooth survival, the need for re-treatment and oral health-related quality of life can be considered tangible patient outcomes. Notably, from the British practice-based cross-sectional study (Sharma et al., 2018), the PROs oral pain/discomfort, dietary restrictions and dental appearance correlated with poor periodontal conditions.

From the literature search and the additional supporting papers, for example (Matuliene et al., 2008, 2010; Salvi et al., 2014) as well as based on biological plausibility, it is clear that periodontitis patients with residual periodontal pockets  $\leq 4$  mm after active periodontal therapy are more likely to have stability of clinical attachment level over a follow-up time of beyond 1 year (Renvert & Persson, 2002). The parameter bleeding on probing was not a significant factor associated with stability of clinical attachment level (Renvert & Persson, 2002). We would like to stress that our purpose of this position paper focused on patient endpoints, and therefore, classical papers providing parameters related to tooth survival or clinical attachment level stability in the absence of bleeding on probing or in the absence of inflammation around teeth or at individual sites were not retrieved, for example (Lang, Adler, Joss, & Nyman, 1990; Schätzle et al., 2004). Matuliene and co-workers identified that *after active periodontal therapy*, residual pockets  $\geq 6$  mm and full-mouth bleeding

scores of  $\geq 30\%$ , represented a risk for tooth loss for the patient (Matuliene et al., 2008).

Although the research base is limited both in quantity and strength, the most reasonable recommendation for developers of guidelines for periodontal therapy is that the achievement of shallow pockets following active periodontal therapy confers the highest chance of stability of periodontal attachment and lowest risk of tooth loss. In that respect, also a recent systematic review concluded that there is insufficient evidence to determine the superiority of different periodontal therapy protocols or adjunctive strategies to improve tooth survival during the periodontal maintenance phase (Manresa, Sanz-Mirallés, Twigg, & Bravo, 2018); no trials evaluated supportive periodontal therapy versus monitoring only.

Whilst the current review has focused on single measures, composite outcomes may have more value in defining desirable endpoints of therapy. Indeed, it was stated in a recent consensus report on prevention issues related to both caries and periodontal diseases that modern preventive practice should focus on the identification of risk in individuals using validated risk assessment tools (Chapple et al., 2017). In a systematic review of risk assessment tools, it was concluded that these tools can identify individuals with different probabilities for the prediction of periodontitis progression and tooth loss after periodontal therapy (Lang, Suvan, & Tonetti, 2015).

In terms of providing a scientific basis for treatment guidelines, it needs to be recognized that the majority of periodontal treatment studies presents relatively short-term results ( $\leq 1$ -year follow-up). Furthermore, there are few data employing PROs. Therefore, recommendations about treatment options should take these limitations into account. A further consideration is that randomized controlled trials (RCTs) on periodontal treatment do not necessarily represent the standard of care in clinical dental practice. In the vast majority of RCTs, they are performed in university settings with unlimited time and where patients undergo multiple recall visits at strict time points (Greenstein, 1993), whilst guidelines are developed for broad use in all kind of dental practices, where the results of academic studies may not be applicable. Currently, efforts are underway to develop a core outcome set of measures for periodontal effectiveness (Lamont, Clarkson, Ricketts, Heasman, & Ramsay, 2017). The core outcome set will be defined by a consensus of key stakeholders including patients, dentists, hygienists/therapists, specialists, clinical researchers and policymakers. Stakeholders will be asked to prioritize outcomes and as such a core outcome set can be established. This will help to create more homogeneity amongst clinical trials, systematic reviews and clinical guidelines (Lamont et al., 2017).

### 4.2 | Considerations on clinical attachment levels

For dental and periodontal researchers who are involved in establishing clinical periodontal treatment guidelines, an important discussion issue is the use and the actual meaning of clinical attachment levels. The assessment of clinical attachment level changes

over time in periodontal sites and averaged for per patient, having received no or any kind of therapy, the relation with histological attachment levels and the appreciation of this measurement for the evaluation of periodontal therapies at the site- and/or patient level (tangible patient outcomes) have been critically addressed (Ryan, 2005). Thus, changes in clinical attachment level measurements are most frequently used as clinical outcomes in clinical trials (Ryan, 2005), and however, in contrast to (university-based) clinical studies, clinical attachment levels are not routinely measured in dental and periodontal practices, and therefore, the value of this parameter needs serious consideration whilst engaged in developing clinical guidelines.

Another discussion point is the concept that at the baseline starting point of clinical studies on active periodontal therapy, most patients and most periodontal pockets with corresponding clinical attachment levels may be likely to be disease-inactive, that is in some sort of state of remission or resolution. True disease activity is most likely sporadic and highly dependent on the variation in the current “fitness” of the immune system<sup>1</sup> in the patient, that is active episodes may be transient (Chapple, Garner, Saxby, Moscrop, & Matthews, 1999; Crawford, 1992; Kinane, Stathopoulou, & Papapanou, 2017; Page & DeRouen, 1992; Papantonopoulos, Takahashi, Bountis, & Loos, 2013). Therefore, it is a challenge to design clinical studies on active periodontal therapy keeping above facts in mind, since the recruitment of study subjects may yield a large majority of patients with chronically inflamed, but not actively progressing periodontal lesions. Clearly, the duration of follow-up and the number of participants required to show meaningful differences in outcomes of clinical attachment levels will be substantial and could constitute a barrier to future research.

#### 4.3 | Remarks on tooth survival after therapy

A further challenge to periodontal outcome research, in general, is the low rate of disease progression for periodontitis patients following treatment enrolled in maintenance care. Only 5% of individuals in periodontal maintenance demonstrated clear disease progression leading to tooth loss over a period of some years of follow-up (Crawford, 1992; Greenstein, 1993; Page & DeRouen, 1992). A more recent systematic review found that the proportion of study subjects that showed no tooth loss during maintenance ranged from 50% to 89% for practice-based studies and from 36% to 80% for university-based studies (Chambrone et al., 2010). A long-term follow-up study ( $9.5 \pm 4.5$  years) showed that about 50% of the patients in maintenance did not lose any tooth (Matuliene et al., 2010).

Tooth loss after therapy is also to a limited degree dependent on the level of compliance during the supportive periodontal therapy (maintenance) (Lee, Huang, Sun, & Karimbux, 2015). Research has

shown that teeth have less risk of being lost during maintenance if patients are more compliant with supportive periodontal therapy (Matuliene et al., 2010), but at the same time, based on studies, there is heterogeneity amongst the data on tooth loss during supportive periodontal therapy (Lee et al., 2015).

A further confounder is that the decision to extract a tooth may not be based on a clear diagnosis of untreatability, but based on other factors. Reports have indicated that teeth may more easily be extracted than before the millennium shift, with a view to replacing teeth with implants, despite the evidence that periodontally involved but well-maintained teeth, out survive—and are cheaper—than implants (Levin & Halperin-Sternfeld, 2013; Schwendicke, Graetz, Stolpe, & Dorfer, 2014). Clearly, there are unidentified variables causing data heterogeneity and affecting the risk of tooth loss, for example different treatment traditions over the last 60 years, geographical variation, dental care reimbursement systems, the popularity of implant therapy and number of remaining natural teeth.

#### 4.4 | Considerations on our current understanding of periodontitis

What has changed over the last 25 years is our understanding of the pathophysiology of periodontitis. Today we understand that periodontitis is an inflammatory disease and that a proportion of the population is susceptible (Bartold & Van Dyke, 2019; Kinane et al., 2017; Loos & Van Dyke, 2020). The susceptible patients have (possibly in an episodic manner) aberrant immune responses leading to temporary disease activity in certain sites, with some progression of periodontal destruction. Already in 1997, Offenbacher et al. mentioned that periodontitis is a multicausal, complex disease (Offenbacher, Salvi, Beck, & Williams, 1997). They questioned what are appropriate outcome measures of trials: using, as we have reviewed here, for example pocket closure ( $\leq 4$  mm), residual pockets (i.e., pockets  $\geq 5$  mm), changes in probing depths, changes in clinical attachment levels or patient proportions of sites with bleeding on probing, are all “fundamentally unidimensional” and may be “mildly informative” at best. The number of deepened or residual pockets or a certain proportion of sites with signs of inflammation are not per se, by themselves, only deterministic for future stability of attachment level or tooth survival, need for re-treatment, or even oral health-related quality of life. Multiple patient factors will be interacting with each other to determine a proper host response being susceptible or resistant to further periodontal destruction, and to make matters even more difficult to grasp is the fact that during a life span susceptibility, resistance and resilience may change (Ebersole et al., 2018, 2016; Larsson, 2017; Loos & Van Dyke, 2020). We should consider the following:

- as patients grow older the immune senescence (“inflammaging”) may play a role;
- the genetic background of the patients including epigenetic changes accrued in a lifetime, which in part determine and change the host resistance blueprint;

<sup>1</sup>The term “immune fitness” is used to describe the current immune responsiveness of a subject, for example the resilience, resistance, tolerance, adaptation and resolution capacities to any challenge, and this is also dependent on genetic, epigenetic factors and age of the patient (Barnig et al., 2019; Botticelli et al., 2017; Ebersole et al., 2018; Ebersole et al., 2016; Larsson, 2017; Loos & Van Dyke, 2020; Te Velde et al., 2016).

- the effect of systemic diseases and medications, such as diabetes and high blood pressure medications or immune-suppressive drugs that effect severely immune responses;
- lifestyle factors such as smoking and dietary habits or availability of proper micronutrients;
- also, whilst we normally score dental plaque in the clinic as present or absent, the effect of the quantity and quality may change over time: where the patient can live in symbiosis with a given microbiota in the subgingival region in a certain period of his/her life, for example over a period of 10 years being in maintenance, this may change due to changes in the immune responses as outlined above.

Taking the multicausality model for the emergence and disease progression of periodontitis one step further to predict the stability of the periodontal condition after therapy, it becomes clear that the factors we discuss in this paper are not simply and unidirectionally determined by, for example, residual pockets depths or some mm's change in clinical attachment level. We urgently need multilevel statistics and multifactorial algorithms including all, and more, host, microbial and local oral and dental parameters, to predict future re-emergence of periodontitis and to estimate local or generalized further breakdown of periodontal tissues (Axtelius, Soderfeldt, & Attstrom, 1999; Gilthorpe, Griffiths, Maddick, & Zamzuri, 2000; Lopez, Frydenberg, & Baelum, 2009; Lundgren, Asklow, Thorstensson, & Harefeldt, 2001; Tu et al., 2004a, 2004b).

Thus, the biology for the results that a high proportion of residual pockets of  $\geq 6$  mm are predictive for instability (i.e., loss) of clinical attachment level (Renvert & Persson, 2002) is today better understood. Deep residual pockets form a favourable niche for biofilms dominated by asaccharolytic, proteolytic and anaerobic pathobionts (Bartold & Van Dyke, 2019; Kilian et al., 2016; Marsh, 2003). They feed on host immunological and inflammatory components, leakage of other plasma proteins and erythrocytes. These subgingival dysbiotic microcosms in deep residual pockets after therapy re-challenge the periodontitis patients who have already demonstrated to have an aberrant immune response, that is the onset of periodontitis has occurred. Today we understand better that from the aspect of creating unfavourable ecological niches for the pathogenic microbiota, the goals of periodontal therapy and subsequent maintenance should be to reduce or eliminate residual probing depths whilst keeping the resistance and resilience of the patient at a high level.

#### 4.5 | Endpoints of periodontal therapy revisited

In this review, we focused on tangible endpoints after active periodontal therapy. Tooth survival, the absence of the need for re-treatment, the maintenance of a sufficient oral health-related quality of life, have been already for half a century, the logical and tangible patient outcomes. However, with our current knowledge, we realize that chronic inflammation of the periodontal tissues (clinically visible as red and swollen gingiva and professionally assessed by bleeding

on probing or noticed by the patients as bleeding after tooth brushing) even when none or when minimal periodontal attachment loss and alveolar bone loss are incurred (e.g., pregnancy gingivitis) may give rise to a systemic inflammation affecting other organs, such as the cardiovascular system or the course of a pregnancy and development of the embryo in utero (Daalderop et al., 2018; Dave & Van Dyke, 2008; Linden, Lyons, & Scannapieco, 2013; Sanz et al., 2019; Schenkein & Loos, 2013). Future endpoints of periodontal treatment may include the absence of systemic signs of inflammation, for example C-reactive protein levels  $< 3$  mg/L; these may suffice as endpoints to consider periodontal treatment successful for the health of the patient, and therefore, for example, tooth loss becomes an indirect or surrogate parameter. And thus, periodontal inflammation as measured by bleeding on probing, and periodontal inflamed surface area measurements (Nesse et al., 2008), could be valid surrogate markers for systemic endpoints.

Nevertheless, tooth loss as an endpoint of periodontal therapy could be questioned today. Tooth loss reflects tooth extractions resulting from a clinician's subjective decision (Levin & Halperin-Sternfeld, 2013) and could be favoured due to the current popularity of implant therapy; however, the tooth extraction is not always indicative of the lack of a tooth to survive in the long term. Today we realize with the arrival of an alternative for a tooth, that is a dental implant, that tooth extractions are indicated much more often by the dental profession. The perceived solution by both the dentist and the patients for loss of a tooth has sparked a worldwide increase in tooth extractions (Levin & Halperin-Sternfeld, 2013).

## 5 | CONCLUDING REMARKS AND RECOMMENDATIONS

Periodontitis is a chronic inflammatory disease in susceptible individuals. Therefore, in addition to tangible clinical outcome measures such as tooth survival, PROs including oral health-related quality of life, continuous functionality and aesthetic appearance are important. From our review, there are only limited data to guide treatment options based either on clinical outcomes or PROs. As more data emerge from periodontitis treatment studies that go beyond investigating pure statistical superiority/equivalence to the relevance of outcomes to the individual, research will be able to better inform treatment choices. In addition, as the effects of chronic periodontal inflammation on other organs and the blood circulation system become more proven, we are likely to have to reconsider the definitions of tangible patient outcomes to include systemic health measures.

### 5.1 | Recommendations for guideline development

The current review of treatment endpoint studies showed, perhaps not unexpectedly, that the body of evidence available for periodontal therapy is largely based on limited studies of

conventional professional surrogate outcomes. By no means, it has been our intention to discard more than 50 years of valuable clinical research in periodontology. However, healthcare (including periodontal health) and its associated research are changing based on further understanding of the disease, research methodology and what research is required by stakeholders (patients, clinicians, policymakers and others) to inform on clinical decision making. The expert and highly experienced periodontal research community will need to work to develop studies that can more closely guide such treatment choices. Involving people living with a condition as co-researchers is also a rapidly developing new paradigm in healthcare. Many governments and other public research funding schemes already require this in order to improve research quality and relevance (Needleman, 2014).

As such, for clinicians and dental researchers who will be engaged in the development of clinical guidelines for periodontal therapy, the following can be recommended:

1. The best available evidence suggests that—following active periodontal therapy—the achievement of shallow periodontal pockets ( $\leq 4$  mm) that do not bleed on probing in patients with full-mouth bleeding scores  $< 30\%$  confers the highest chance of stability of periodontal health and lowest risk of tooth loss. Developers of guidelines for periodontal therapy can apply the current pathophysiological paradigm that shallow periodontal pockets after active periodontal therapy (non-surgical and surgical therapy) are providing the least hazardous ecological sites for the re-outgrowth of a dysbiotic biofilm and therefore for the patient to have a better chance for further long-term stability of his/her periodontal attachment.
2. Guidelines for periodontal therapy should take into consideration tangible clinical outcomes (tooth survival, reduced need for re-treatment) and PROs including oral health-related quality of life, no pain (i.e., lack of discomfort), improved, or at least continuous, dental functionality, improved aesthetic appearance and a general quality of life.
3. Both short-term ( $< 12$  months) and long-term treatment outcome studies are needed. Short-term studies are particularly valuable in early-stage research to determine promising therapies. Long-term studies, which might include both experimental (RCTs) and observational designs, will better guide treatment options of a chronic condition such as periodontitis.
4. In the process of developing guidelines for periodontal therapy, in the evaluation of “best practice” effects on clinical attachment levels, the proportion of threshold changes such as  $\geq 2$  mm or  $\geq 3$  mm in clinical attachment levels are preferable, rather than mean changes in this parameter; for the vast majority, mean differences in changes of clinical attachment levels between two or more treatment modalities reported in many treatment studies are considered by many dental professionals to be clinically insignificant.

Guidelines will need to increasingly recognize and embrace the heterogeneity amongst patients and, therefore, the individuality of

patients' response to therapy, and in addition, to the changes within an individual over time. Hence, the concepts of precision medicine are likely to influence periodontal therapy choices.

## 5.2 | Recommendations for future studies

In addition to the observations above we propose the following:

1. Design long-term large population-based studies on the efficacy of periodontal therapies employing both tangible clinical outcomes and PROs that consider today's understanding that periodontitis is a complex inflammatory disease, probably episodic in nature and with multiple causal factors that play a role simultaneously and interact with each other.
2. Involve patients and caregivers as part of the research team to design studies. People living with a condition are uniquely qualified and expert to be able to contribute to improving the quality and relevance of treatment outcome research.
3. The patient *after his active periodontal treatment* should be the unit of study, where a range of demographic, biometric, co-morbidities and lifestyle factors should be noted, in conjunction with tangible PROs such as tooth survival, no pain, continuous dental functionality, no need for periodontal re-treatment, aesthetic appearance and oral health-related quality of life. Implementation of big data analyses and bioinformatic tools are needed. The move to electronic/digital health records in many clinical settings offers the possibility of such data availability. For example, a European organized database consisting of several million periodontal patients entered after their active periodontal therapy could yield the type of data to address questions more relevant to precision medicine. The personal prediction of risk for disease exacerbation is currently being suggested and explored (Divaris, 2019; Weng, Vaz, Qureshi, & Kai, 2019).

## CONFLICT OF INTEREST

The authors have no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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