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REVIEW ARTICLE

Clinical periodontal diagnosis

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1 | INTRODUCTION

Periodontal diseases encompass pathological conditions of the tooth supporting structures initiated by the presence of bacterial biofilms eliciting a host response.[1–4] Following destruction of supracrestal connective tissue, further loss of periodontal ligament fibers may result in loss of the alveolar bony support. From a clinical point of view, this condition may be recorded as loss of clinical attachment in relation to the cemento-enamel junction (CEJ) and be associated with an inflammatory reaction in the gingiva clinically detectible as erythema, swelling, and bleeding on probing (BoP). Additional signs may include formation of periodontal pockets, recessions of the gingival margins, involvement of furcation areas, and, eventually, radiographic alveolar bone loss. Finally, patient-reported complaints such as increased mobility, tooth migration, and tilting may also be part of the diagnostic process.

Clinical periodontal diagnosis is based upon the recording and interpretation of the above-mentioned clinical signs and symptoms in an attempt to establish extent and severity of the disease in the entire dentition. It should be realized, however, that based on clinical parameters, periodontal diagnosis can only be established following the biological onset of the disease process. This means that clinical onset of disease as well as periods of progression or remission at the tooth or site level may be unknown to the clinician. This is corroborated by the fact that outcomes from preclinical and clinical studies indicate that periodontitis progresses by periods of exacerbation and remission.[5,6]

Today, routine clinical diagnostic methods aimed at detecting with high predictability periods of exacerbation or remission of disease are lacking. Rather, periodontal diagnosis is based on clinical and radiographic signs which may not reflect the presence of an active disease process but the sequelae of a previous pertubation of the host defense mechanisms.

Therefore knowledge of subclinical signs of disease activity and pathogenetic mechanisms also affect the interpretation of epidemiological data on the prevalence of periodontal diseases and their treatment modalities.

Despite all the limitations of contemporary diagnostic methods listed above, critical interpretation of clinical and radiographic parameters enable the clinician to routinely appraise the status of the periodontal patient.

More important to the patient, however, is the fact that clinical periodontal diagnosis requires the implementation of an appropriate treatment strategy. In this respect, the consensus report of the 2017 World Workshop[4] guides the clinician in classifying the periodontal patient. In addition, a diagnosis for each individual tooth forms the basis of a pretherapeutic prognosis and the establishment of a comprehensive treatment plan for the individual patient.

Eventually, the long-term goals of periodontal therapy focus on the preservation of sufficient periodontal tissue support capable of maintaining a functional dentition for a lifetime. It is understood that such treatment goals may only be achieved through the combination of optimal self-administered biofilm control by the patient and delivery of high-quality comprehensive therapy by dental professionals.

It is the aim of this review to present a summary of subjective and objective criteria required to classify patients with periodontal health or disease as well as to assign a diagnosis to every single tooth.

2 | GENERAL AND DENTAL HISTORY

2.1 | Patient's chief complaint and expectations of treatment

Particular attention should be payed to the patient's chief complaint and expectations of treatment. Such expectations have to be taken seriously and must be incorporated in the evaluation of the clinical situation. Patients, however, may express specific desires and expectations regarding treatment outcomes that may be incongruent with the true assessment by a dental professional with respect to the clinical situation. Satisfactory treatment outcomes may only be achieved if the patient's expectations are in balance with the objective evaluation of the extent and severity of the disease.

2.2 | Patient's dental history and complaints

The assessment of complaints and symptoms of disease represent a starting point and central part of the patient's dental history. These aspects include an assessment of previous dental care and maintenance visits if not specified by the referring dentist. In this context, information regarding signs and symptoms of periodontal diseases noted by the patient such as tooth migration or elongation and increasing mobility, bleeding gums, food impaction, and impaired chewing ability should be evaluated. Outcomes from a recent retrospective analysis, however, indicated that recognition of true periodontal chief complaints by the patient such as bleeding gums, tooth mobility, and alterations in gingival color/shape was low.[7]

Improvements in chewing comfort including the need for tooth replacement with removable or fixed dental prostheses should also constitute an integral part of the comprehensive treatment plan.

2.3 | Assessment of the medical history

In order to make a personalized treatment plan for each patient, his or her medical history is of great importance. Prior to initial examination, a health questionnaire must be filled out and signed by every patient. In order to evaluate the potential risk factors for routine periodontal therapy, general medical conditions and medications should be covered in this questionnaire. Moreover, an interview with the patient can give additional information regarding unclear risks or unknown conditons. Further uncertainties or missing information which cannot be provided by the patient should be discussed with the patient's physician. A written medical report from the physician is very useful in patients with complex health conditions. The assessment of the medical history will help the clinician regarding the following important issues:

- Protections of the dental team and other patients against infectious and contagious diseases
- General risk assessment
- Protection of the patient against systemic effects of routine therapy
- Control and/or knowledge of patient's modifiable and non-modifiable risk factors for successful comprehensive dental treatment
- Pain and anxiety control

2.4 | Assessment of family and social history

Prior to a detailed assessment of the clinical condition, it is of paramount importance to verify the patient's social environment and to gain a sense for his/her priorities in life, including his/her expectations and desires from both periodontal and implant therapy. In addition, specific questions aimed at revealing the presence of periodontitis (i.e., aggressive periodontitis; Stage II-IV, Grade C) within the family should be always taken into consideration.

2.5 | Assessment of oral hygiene habits, self-performed biofilm control, and smoking history

Due to the importance of self-performed biofilm control to successfully treat periodontitis, a concomitant accurate evaluation of patient's routine dental care, including frequency and duration of daily tooth-brushing procedures has to be performed. Moreover, patient's awareness of interdental cleansing devices, chemical supportive agents, and regular utilization of fluorides should be evaluated.

Since cigarette smoking has been documented to be the second most important risk factor after inadequate self-performed biofilm control in the etiopathogenesis of periodontal diseases,[8] the importance of smoking counseling should not be underestimated. Furthermore, since cigarette smokers have been shown to be at higher risk of developing peri-implant biological complications,[9] implant loss,[10] and peri-implant marginal bone loss,[11] proper assessment of smoking history and habits should be performed for every candidate for implant therapy.[12,13] Finally, it has be underlined that the determination of smoking status should include detailed information including exposure time and quantity.

3 | SIGNS AND SYMPTOMS OF PERIODONTAL DISEASES

3.1 | Extraoral features

Dentists should be aware of the importance of an extraoral examination. The extraoral examination may include the assessment of skin, face, lymph nodes, odors from body and breath, and joints and muscles of the head and neck region. The palpation of the cervical lymph nodes is recommended to identify possible lymphadenopathies. In a healthy status, lymph nodes are not palpable. If an obvious reason (e.g., acute infection) may cause the enlargement of

lymph nodes, the position, size, and mobility should be included in the patient's history. A temporomandibular joint (TMJ) examination is also important to detect parafunction. Possible extraoral findings for periodontal abscesses are facial swelling (3.6%), elevated body temperature, malaise, regional lymphadenopathy (7%–40%), or increased blood leukocytes (31.6%).[14] For necrotizing periodontal diseases, typical extraoral signs are halitosis (84%–97%), adenopathy (44%–61%), and/or fever (20%–39%).[14] In case of persistence of the enlargement or an unclear cause for swelling of the lymph nodes, the patient should be referred to his/her physician.

3.2 | Assessment of pocket probing depth

The distance from the free gingival margin (FGM) to the bottom of the gingival/ periodontal pocket is termed pocket probing depth (PPD). Like clinical attachment level (CAL), PPD is assessed to the nearest millimeter on all tooth surfaces by means of a standardized and graduated periodontal probe.

PPD should be assessed at all surfaces of all teeth present as well as at existing implants in the oral cavity. PPD is the major contributor to the documentation of the periodontal lesions as depicted in a periodontal chart.

The periodontal chart represents the key diagnostic tool to be used for an immediate evaluation of diseased sites from an extent and severity perspective. The periodontal chart may also be used in case presentations and discussions with the patient. Hence, it is a two-dimensional visualization of the health/disease status of the periodontal tissues.

For convenience, the clinician is referred to a charting template offered free of charge by the University of Bern, Switzerland, Department of Periodontology, with the following link: www.perio dontalchart-online.com. This site is available in 33 languages and explains in detail how to perform a correct chart that may be downloaded for the patient record.

Clinical probing of implant sites represents a sensitive diagnostic procedure for the detection of peri-implant diseases. It has to be realized that peri-implant probing is "a must" in monitoring implants over time. The minor trauma left to the peri-implant soft tissue seal after probing has been shown to completely repair with a new junctional epithelium after 5–7 days following probing.[15] Hence, there is no adverse effect to the establishment of the soft tissue adhesion mechanism around implants.

PPD represents the severity and extent of the periodontal lesions and is indirectly a measure of the inflammatory burden of the patient. Generally, PPD should be related to the reference of the attachment level, that is, the CEJ. Only by comparing PPD with CAL can an objective assessment of the extent and severity of periodontitis affected dentitions may be obtained.[16]

It is evident that PPD is affected by the presence or absence of inflammation within the tissues. Edema may cause swelling and a coronal displacement of the gingival margin and result in the formation of a pseudo-pocket. On the other hand, shrinkage of the gingival tissues may be the result of, for example, successful periodontal therapy with concomitant reduction in inflammation. Hence, it is advisable to always evaluate PPD together with CAL in order to assess the periodontal condition in detail.

3.3 | Clinical errors inherent to periodontal probing

The determination of CAL and PPD is largely dependent on the instrument used for the examination and the technique applied to assess the tissues. Clinical probing around teeth and implants is considered to be a fairly accurate clinical estimate for the evaluation of periodontal or peri-implant lesions, although some inherent inaccuracies in the evaluation have been recognized for many years.

The tip of the periodontal probe is considered to identify the most apical cell of the junctional (dento-gingival or implanto-mucosal) epithelium. Yet, research has indicated that this is rarely the case, and some inaccuracies are inherent to the probing procedure.[17–24]

At least five factors may affect the readings of CAL and PPD: (i) thickness of the probe at the tip, (ii) angulation and positioning of the probe, (iii) graduation scale of the probe, (iv) pressure applied to the probe, and (v) degree of inflammation of the periodontal tissues as an expression of the density of the collagenous tissue seal. It is evident that only a histological examination will determine the accurate anatomical level of the periodontal attachment and the apical extension of the periodontal pocket.

Obviously, clinical assessments of CAL and PPD represent surrogate variables to the histologically documented situation. Measurement errors depend up on factors like the thickness and taper of the probe, incorrect angulation or positioning of the probe, and the graduation scale of the probe and may be minimized by choosing standardized probes and careful examination techniques. Usually probes with a tip diameter of 0.4–0.5 mm are selected for assessment.

Measurement errors as a consequence of variation in probing pressure and/or the variation in the extent of inflammatory infiltrate within the soft tissue seal are more difficult to control. Logically, the higher the probing pressure applied, the deeper the probe will penetrate into the soft tissue seal. Studies performed to identify the variations in probing pressure (force) applied by clinicians have yielded probing pressures from 0.03–1.3 N.[25] Moreover, probing pressures varied as much as 2:1 for single clinicians on repeated applications.[26] To minimize the errors encountered when applying various probing pressures, so-called pressure-sensitive probes have been proposed. These probes are generally preset to a probing pressure of 0.3 N.[20,27]

Over- or underestimation of both PPD and CAL may occur as a result of the presence or absence of an inflammatory infiltrate subjacent to the junctional or pocket epithelium.[17,20,21] When the connective tissue subjacent to the pocket epithelium is infiltrated by inflammation, the periodontal probe will penetrate beyond the apical termination of the dento-gingival or implanto-mucosal epithelium resulting in an overestimation of the "true" pocket depth. Conversely, for example, after successful periodontal therapy, when

the inflammatory infiltrate is minimal or even absent, the newly formed collagenous tissue in the area previously affected by the infiltrate will result in a dento-gingival or implanto-mucosal unit that is more resistant to probe penetration; hence, the probing measurements of PPD and CAL may underestimate the "true" histologically defined levels.

3.4 | Assessment of CAL

CAL documents the extent and severity of the periodontal lesion. The clinical attachment has been lost as a consequence of the microbial dysbiosis resulting in a host response that led to the loss of connective tissue fiber attachment to the tooth. It is an irreversible damage to the supporting apparatus of the tooth that, without any regenerative efforts, will be lost for the life of a tooth.

CAL is usually measured to the nearest millimeter applying a standardized and graduated periodontal probe. The reference is the CEJ as the apical extension of the junctional epithelium in a pristine tooth without prior pathological tissue changes terminates at the CEJ. Consequently, the distance from the CEJ to the bottom of the probable gingival/periodontal pocket is measured. The choice of the proper instrument is crucial in determining the accuracy of the clinical assessment.

To determine the CAL, it is necessary to provide two clinical measurements: (i) the distance from the FGM to the CEJ for each tooth surface that is to be assessed, and (ii) the PPD, again, assessed to the nearest millimeter. CAL is calculated by subtracting the distance of FGM-CEJ from PPD whenever the CEJ is covered by the soft tissue. In case of gingival or mucosal recessions, the distance from the FGM to the CEJ becomes negative; hence, the calculation for CAL turns into an addition of this distance (FGM-CEJ) to the PPD.

3.5 | Assessment of BoP

BoP has been shown to represent a diagnostic clinical test to document the inflammatory status of the dento-gingival or implanto-mucosal unit.

A periodontal probe standardized for its dimensions and preferably insertion pressure is inserted to the bottom of the gingival/periodontal pocket by applying a light force.[28] The force to be used has been identified to be 0.2-0.3 N. This will avoid false positive readings and identify the tissues bleeding due to the presence of inflammation and not due to an applied trauma. The 0.3 N are to be applied both in pristine and/or homeostatic tissues, that is, intact height of the periodontium[29] as well as in tissues that have experienced periodontitis and were successfully treated, that is, a reduced periodontium.[30]

If bleeding is provoked by running a probe along the gingival margin,[31] the true tendency to bleed from the depth of the pocket is overlooked.

If bleeding is provoked upon retrieval of the probe within 10 s, the site is considered BoP-positive and, therefore, clinically inflamed. This simple dichotomous score is preferred by the clinicians over more elaborate and more accurate gingival indices.[32]

Usually, BoP is determined at four or six surfaces of all teeth and/or implants, and the mean percentage of BoP-positive sites for the individual is calculated. While BoP-positive sites at teeth represent gingivitis, BoP-positive sites at implants reflect the presence of mucositis. The higher the BoP score obtained, the more generalized the inflammatory status becomes.

Obviously, BoP represents a reversible inflammatory parameter that may be affected by prophylactic measures, that is, oral hygiene and biofilm removal.[33,34] As gingivitis represents a precursor for periodontitis, mucositis represents the precursor for peri-implantitis (Figure 1).

3.6 | Assessment of furcation involvement

Periodontal pockets are usually defined as one-, two-, or three-wall bony pockets, the fourth wall being defined by the tooth surface. If the disease has progressed into the furcation area of a multi-rooted tooth, the roof of the furcation limits the lesion on three sides, and the alveolar bone forms the lower limit of the lesion. Hence, a furcation involvement (FI) represents a periodontal lesion oriented in a horizontal rather than a vertical direction. As FI teeth are difficult to treat and maintain healthy by prophylactic measures, the identification of such teeth is of utmost importance for the assessment of periodontal status.

Furcation entrances of all molars and first premolars of the maxilla should be assessed with a curved furcation probe (i.e., Nabers furcation probe) usually with graduations at 3 and 5 mm. The horizontal component of probing is graded (0–3) according to the following criteria:

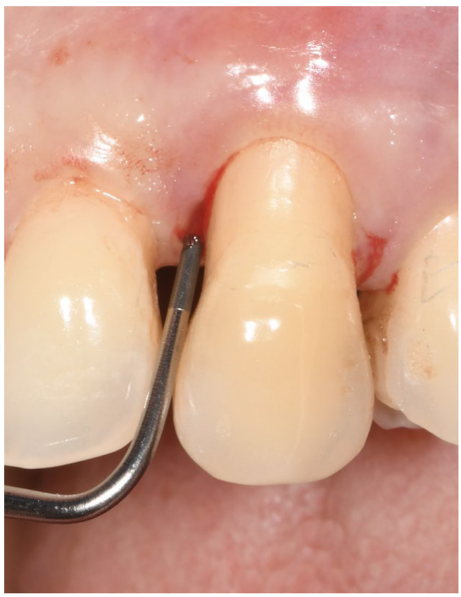

FIGURE 1 Assessment of pocket probing depth in conjunction with bleeding on probing. A graduated Michigan periodontal probe is inserted to the bottom of the periodontal pocket and is moved along the root surface.

Grade 0 = Furcation not probable.

Grade 1 = Furcation with a horizontal component of probing ≤3 mm. (superficial FI).

Grade 2 = Furcation with horizontal probing of >3 mm (at one entrance of the furcation) (deep FI).

Grade 3 = Furcation with through and through opening (horizontal probing of >3 mm from at least two entrances).

The degree of the FI is charted using circles as a symbol. An open circle (o) (Grade 1), a semicircle (⊖) (Grade 2), and a filled in circle (•) (Grade 3).

3.7 | Assessment of tooth mobility

In 1938, S.C. Miller developed the most commonly used clinical method for determining tooth mobility (TM). Using his method, the tooth is held firmly between two instruments and moved back and forth and mobility scored on a scale of 0 to 3. A score of 0 denotes no detectable movement when force is applied, other than what is considered normal (i.e., physiologic) motion (<0.2 mm). A score of 1 indicates mobility greater than normal. Mobility of up to 1 mm in a buccolingual direction is scored 2. Movement of more than 1 mm in a buccolingual direction combined with the ability to vertically depress the tooth is scored 3.[35,36]

Methods for automatic simultaneous recording of tooth loading and subsequent displacement have been used to evaluate the effects on tooth mobility of various treatments of advanced periodontitis, as exemplified by Grabec and co-workers.[37] Their instrument included a pneumatically driven probe and incorporated sensors to detect tooth mobility and loading force. However, in daily clinical practice these more technically advanced and automated instruments seem not as yet to have been widely adopted.

In the literature following the 2017 World Workshop on the classification of periodontitis, in addition to stage III severity a high level of tooth mobility (≥2) worsens the periodontitis to stage IV.[38]

Tooth splinting has been reported to be performed as an adjunctive intervention for teeth with a progressive increase in tooth mobility in order to improve the patient's chewing capabilities.[39]

In a recent systematic review, Helal and co-authors reported on predictors for tooth loss in periodontitis patients.[40] Among other factors, tooth mobility was reported to be significantly associated with tooth loss; however, the heterogeneity was high between the four studies included for the analysis of tooth mobility.[41–44]

3.8 | Assessment of static and dynamic occlusion and temporo-mandibular disorders

Static occlusion refers to the contacts between the teeth when the jaw is closed and stationary, whereas dynamic occlusion refers to occlusal contacts made when the mandible is moving. In an attempt to report on the methods used by dentists for registration of occlusal contacts, a survey was conducted and an anonymous questionnaire was electronically distributed to 2014 randomly selected dentists. The response rate was low (14.87%). In their clinical practice, the responding dentists most often (52.45%) used articulation paper as an indicator for occlusion. Articulation foil was used by 26.22% and articulation silk by 16.78%. The respondents expressed a growing interest in using digital methods when (<0.2 mm) made available.[45]

The co-morbidity of periodontitis and rheumatoid arthritis (RA) is well recognized, especially in recent scientific literature.[46,47] Temporo-mandibular disorders (TMDs) are a frequent finding in the RA patient. Temporo-mandibular joint function was reported to be abnormal in 98.4% of the RA patients, and 62.9% of them presented moderate or severe TMDs.[47] Alertness of dental professionals to TMD pain and periodontal inflammation is strongly recommended.

TMDs are a significant public health problem affecting approximately 5%–12% of the population. TMDs are the second most common musculoskeletal condition after chronic low back pain resulting in pain and disability. Pain-related TMDs can impact the individual's daily activities, psychosocial functioning, and quality of life (National Institute of Dental and Craniofacial Research).

3.9 | Diagnostic criteria for TMDs

The newly recommended diagnostic criteria for TMDs protocol includes both a valid screener for detecting any pain-related TMDs as well as valid diagnostic criteria for differentiating the most common pain-related TMD (sensitivity ≥0.86, specificity ≥0.98) and for one intra-articular disorder (sensitivity of 0.80 and specificity of 0.97).[48] The model has been adopted for general dentistry to identify, diagnose, and treat patients for related orofacial pain. According to the Axis protocol, all patients being examined for the first time, or at follow-up examinations, are asked to answer three simple screening questions (3Q/TMD): (1) Does it hurt once a week or more often in the temple, face, temporo-mandibular joint or jaws? (2) Does it hurt once a week or more often when you yawn or chew? (3) Do you have locking or hooking in the temporo-mandibular joint once a week or more often? If the patient answers "Yes" to one or more of these questions, the patient should be offered a full examination and subsequent treatment.

3.10 | Radiographic analysis

Without any doubt, the clinical periodontal examination provides the clinician fundamental information with respect to PPDs, gingival recessions, quantity and quality of attached gingiva, and FI. Nevertheless, it cannot disclose the status of the alveolar bone which is of crucial importance to precisely diagnose different periodontal conditions. Among the available ionizing modalities, the use of periapical images is by far the most commonly used non-invasive technique in dentistry to inspect the alveolar bone. More specifically, periapical radiographs provide relevant information including subgingival calculus deposits, root morphology length and proximity, periapical lesions, and the

amount of alveolar bone destruction (Figure 2A,B).[49] Furthermore, to enable meaningful comparative analysis and increase reproducibility of the radiographs a long-cone paralleling technique is recommended.[50] However, clinicians should be aware of the limitations of 2D radiographic images during the diagnostic phase such as:

- Lack of detection of periodontal pockets
- Lack of detection of tooth mobility
- Lack of discrimination between the buccal and lingual aspects of tooth and bone
- Significant radiographic changes are visible only after advanced clinical attachment loss
- Radiographic changes are visually detectable when 30%–50% of the bone mineral content has been resorbed.[51]

In recent years, especially to overcome these limitations, utilization of cone beam computed tomography (CBCT) has been rapidly increasing. CBCT has become an integral tool for researchers and clinicians, mostly applied to the implant field. As such, the use of CBCT imaging for the diagnosis of periodontitis has also been evaluated. However, in 2017, the American Academy of Periodontology (AAP) reported that, even though its use may be beneficial in selected cases, there is limited evidence to support the use of CBCT for the different types of bony defects, and there are no guidelines for its application to periodontal treatment planning (Figure 3).

4 | SINGLE TOOTH DIAGNOSIS

Based on the clinical and radiographic conditions assessed through a comprehensive periodontal examination (i.e., periodontal chart and radiographs), five different diagnoses regarding the periodontal condition may be given for every single tooth in the dentition.

A correct diagnosis for every individual tooth should form the basis for a pretherapeutic prognosis and the establishment of a comprehensive treatment plan of the individual patient.

4.1 | Periodontal health

According to the 2017 World Workshop on the Classification of Periodontal Diseases and Conditions (Figure 4), four levels of periodontal health were proposed[52]:

1. Pristine periodontal health characterized by a structurally sound and uninflamed periodontium
2. Periodontal health characterized by a structurally and clinically intact periodontium
3. Periodontal disease stability on a reduced but healthy periodontium
4. Periodontal disease remission/control on a reduced but healthy periodontium.

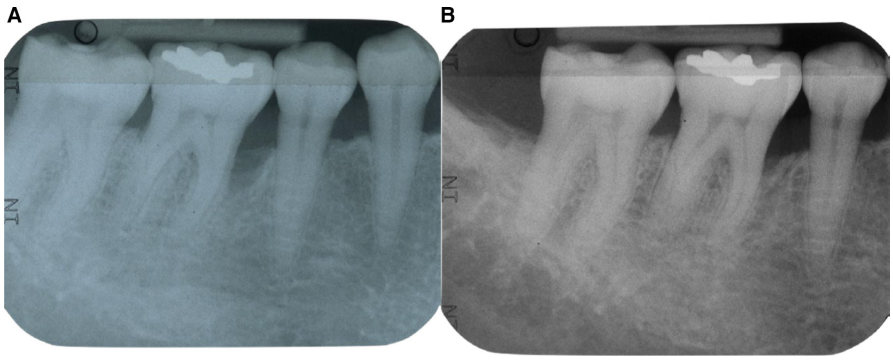

FIGURE 2 A, Radiographic scenario of an infrabony defect on the mesial aspect of tooth 46. B, Periapical radiograph at the 12-month follow-up examination following non-surgical mechanical instrumentation documenting radiographic bone fill.

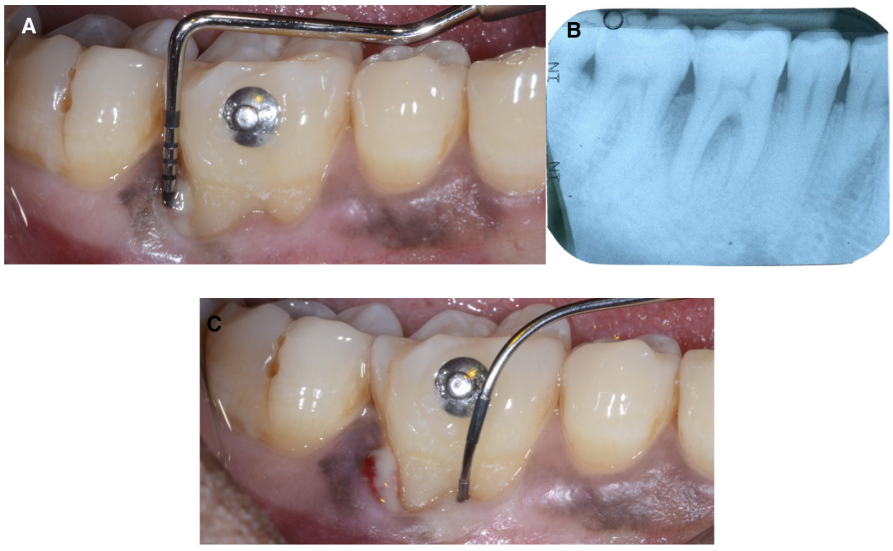

FIGURE 3 A–C, Clinical and radiographic scenarios of a combined infrabony and interradicular defect (i.e., increased pocket probing depth, furcation involvement, bleeding on probing, suppuration, and radiographic evidence of alveolar bone destruction).

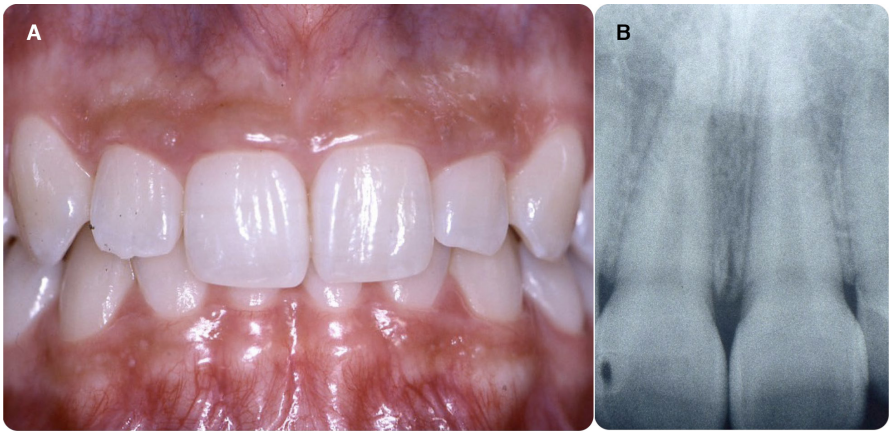

FIGURE 4 A and B, Periodontal health characterized by a clinically and radiographically intact periodontium.

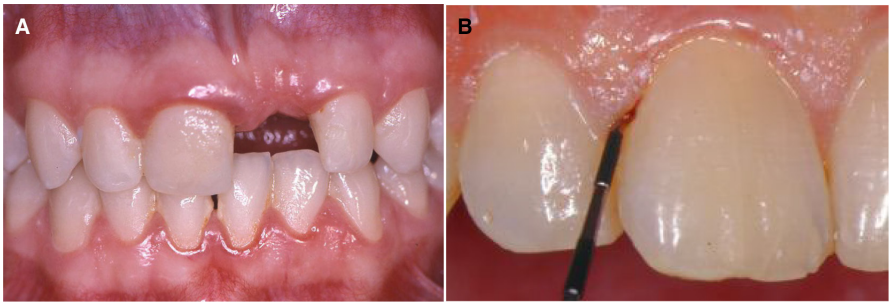

FIGURE 5 Clinical signs of gingivitis. A, Presence of supragingival biofilm and calculus resulting in erythematous and edematous gingival margin. B, Pocket probing depth of 3 mm with bleeding on probing.

4.2 | Gingivitis - tooth level

The diagnosis of gingivitis is applied to teeth displaying BoP without CAL loss. The sulcus depth usually ranges between 1 and 3 mm irrespective of the level of clinical attachment. So-called pseudopockets may be present in cases of increased probing depth without concomitant loss of clinical attachment and alveolar bone and presence/absence of BoP. The diagnosis of gingivitis usually characterizes periodontal lesions confined to the gingival margin (Figure 5).

4.3 | Moderate periodontitis - tooth level

Gingivitis in combination with clinical attachment loss is termed periodontitis. In cases of PPD ≤6 mm, a diagnosis of mild–moderate periodontitis may be given irrespective of the morphology of periodontal lesions. This diagnosis may, therefore, be applied to teeth characterized by a horizontal pattern of alveolar bone loss, thus representing suprabony lesions and/or to teeth characterized by an angular or vertical loss of alveolar bone, thus representing infrabony lesions. Infrabony lesions include defects with 1, 2, and 3 bony walls as well as craters between two adjacent teeth (Figure 6).

4.4 | Severe periodontitis - tooth level

In cases of PPD>6 mm, a diagnosis of severe periodontitis is given irrespective of the morphology of the osseous lesion. As for mild–moderate periodontitis, horizontal as well as angular/vertical alveolar bone loss are included in this diagnosis. The distinction between mild–moderate and severe periodontitis is solely based on increased PPD (Figure 7).

4.5 | Interradicular periodontitis

The adjunctive diagnosis of interradicular periodontitis may be given to multirooted teeth with superficial or deep FI (Figure 8).

In the presence of necrotizing/ulcerative and acute (i.e., gingival and periodontal abscesses) lesions, these terms may be added to the tooth-related diagnosis (Figure 9).

5 | CLINICAL INVESTIGATIONS

5.1 | Non-biofilm-induced gingival and periodontal conditions

While biofilm-induced gingival and periodontal inflammatory lesions are very common, non-biofilm-induced gingival and periodontal manifestations of systemic diseases are rather rare and often present with both distinctive clinical features and characteristics in the patient history. The diagnosis of these disorders is challenging as many of them present with similar clinical findings. To succeed in the diagnosis, a profound knowledge of clinical oral and systemic characteristics of the respective disorder and an interdisciplinary approach is often crucial.

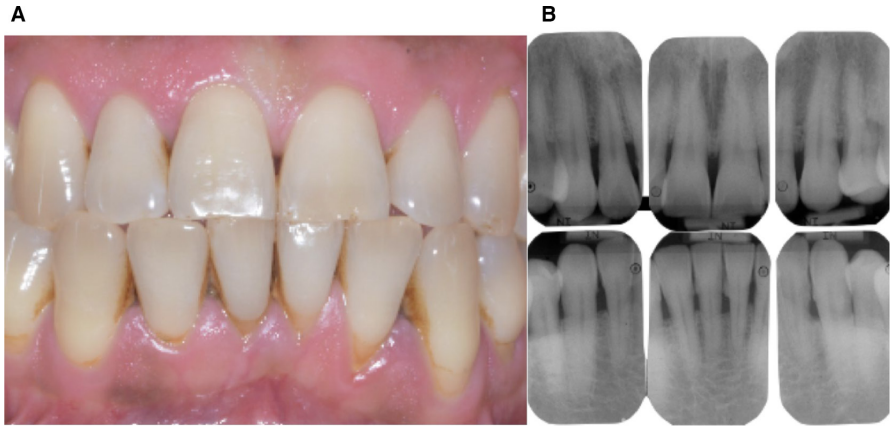

FIGURE 6 Clinical A and radiographic B evidence of mild–moderate periodontitis (i.e., presence of supra- and subgingival calculus and radiographic evidence of horizontal alveolar bone destruction).

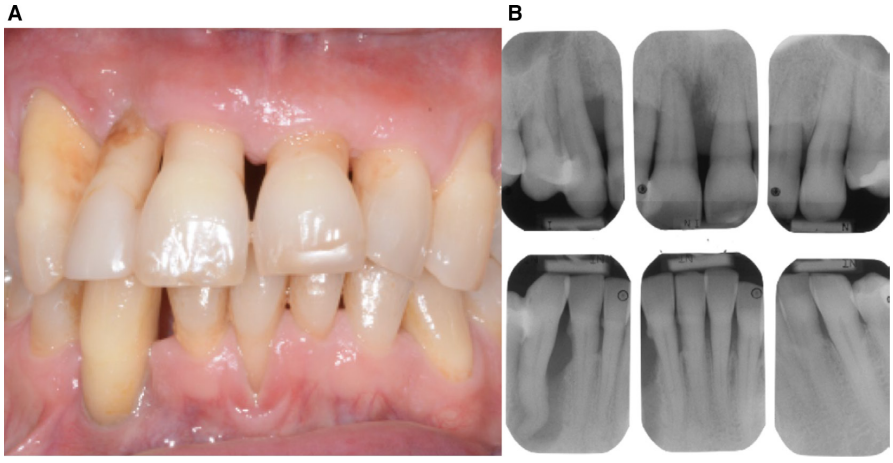

FIGURE 7 Clinical A and radiographic B evidence of severe periodontitis with increased tooth mobility, tooth migration, gingival recessions, and presence of horizontal and angular alveolar bone destruction.

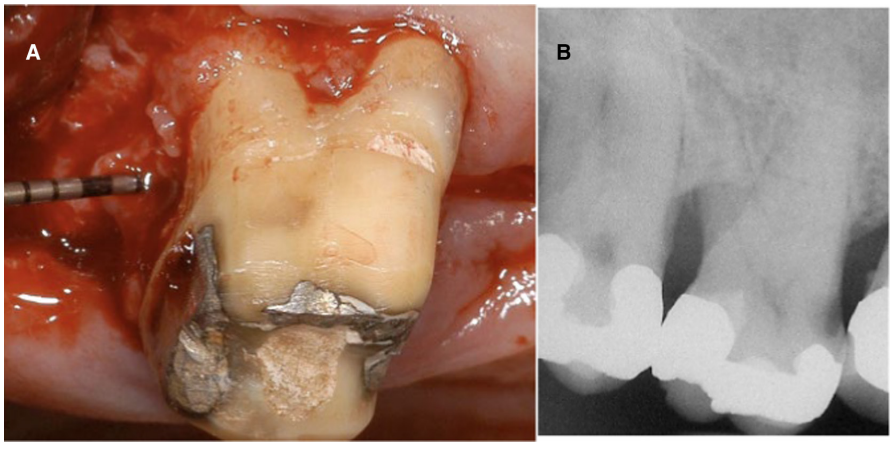

FIGURE 8 Clinical A and radiographic B evidence of Grade 2 furcation involvement at the distal aspect of tooth 16. Secondary caries on the mesial aspect of 16 is also diagnosed.

One of the clinical hallmarks of non-biofilm-induced gingival and periodontal conditions is that they do not resolve or not completely after plaque control. Non-biofilm induced gingival and periodontal lesions and systemic diseases that present in the periodontium can have numerous causes, based on which a classification was established that was revised at the 2017 World Workshop on the Classification of Periodontal Diseases organized by the American Academy of Periodontology and the European Federation of Periodontology.[53,54] Most of these conditions are genetic, others are acquired or inflammatory in nature (Tables 1 and 2). This review concentrates on clinical oral findings and investigations for non-plaque-induced gingival and periodontal conditions. However, to recognize these the clinician needs to cast the net wider and understand the whole picture of the disease/condition.

5.1.1 | Gingival diseases: non-biofilm-induced

Non-biofilm-induced gingival diseases are limited to the gingiva and have been listed at the 2017 World Workshop (Table 2).[55]

Hereditary gingival fibromatosis

Gingival overgrowth, also called gingival hyperplasia or gingival fibromatosis is a well-known side effect of phenytoin, ciclosporine,

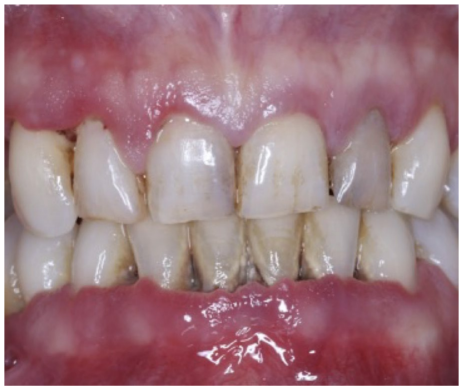

FIGURE 9 Clinical evidence of necrotizing periodontitis in the upper and lower anterior areas with presence of supragingival biofilm, calculus, and interproximal periodontal tissue destruction.

and with calcium channel blocker medication[57]; however, it can also be of genetic origin and is then called hereditary gingival fibromatosis (HGF). HGF can occur as an isolated phenomenon or as part of a syndrome including hypertrichosis, mental retardation, epilepsy, growth retardation, and abnormalities of the extremities.[58] HGF presents with progressive slow, non-hemorrhagic, fibrous, albeit painless growth of the gingival tissue and affects approximately 1 in 750,000 live births.[59] Hitherto the disorder has been mapped to five candidate genes including the Son of Sevenless genes, REST, ZnF862, Alk, and CD36.[60–62] One of the main pathogenic mechanisms results in an excessive secretion of transforming growth factor- (TGF) β and an extensive production of extracellular matrix proteins which clinically manifests as more or less severe enlargement of the gingiva; in severe cases, major parts of the tooth surface might be covered.[63]

Clinical findings: The gingiva present with enlargement that usually becomes obvious at the time of tooth eruption. In cases of early and severe manifestations, tooth eruption might be impacted. Diastema, mispositioning of teeth, cross and open bites are frequent observations. Due to the gingival enlargement, plaque accumulation may increase favoring gingival and periodontitis. Treatment consists of good plaque control and gingivectomy. HGF cannot be cured and often retreatment is required.[64]

Clinical investigations: HGF often accumulates within families. Therefore, a thorough patient and family history is mandatory. Histologic assessment of excised gingival tissue generally reveals increased an amount of collagen fibrils and significant epithelial rete pegs. Blood tests are not indicated as no specific marker or gene mutation is indicative for the disorder.[54]

Bacterial infections

Non-biofilm-induced infections of gingival tissues are very rare and might affect immunocompromised individuals or individuals where the homeostasis between host defense and non-plaque related bacteria is disturbed. Acute infective gingivitis or stomatitis might occur after infection with *Neisseria gonorrhea*, *Treponema pallidum*, *Mycobacterium tuberculosis*, or other pathogens.

TABLE 1 Overview of gingival and periodontal conditions as they were classified at the 2017 World Workshop highlighting the non-biofilm-induced conditions and manifestations of systemic diseases.

Gingival and periodontal conditions	
Periodontal health, gingival diseases and conditions	**Periodontal health & gingival health**
	Gingivitis: Dental biofilm-induced
	Gingival diseases: Non-dental biofilm-induced
Periodontitis	Necrotizing periodontal diseases
	Periodontitis
	Periodontitis as a manifestation of systemic disease
Other conditions affecting the periodontium	**Systemic diseases or conditions affecting the periodontal supporting tissues**
	Periodontal abscesses and endodontic-periodontal lesion
	Mucogingival deformities and conditions
	Traumatic occlusal forces
	Tooth and prosthesis related factors

Clinical findings: These infections manifest as painful edematous ulcerations, as asymptomatic mucous patches, or atypically as highly inflamed gingivitis or stomatitis. In cases of syphilis, multiple ulcerated lesions may appear on lips, tongue, or the hard palate. Some patients with undiagnosed syphilis may first present with oral lesions.[65] Oral tuberculous lesions have become very rare.[66] They appear mostly as secondary lesions often associated with pulmonary disease.[67] Here oral lesions usually present as single, painful, and irregular ulcers covered by inflammatory exudate affecting most often the dorsum of the tongue. However, they may also occur on any other site of the oral mucosa and in a variety of forms such as nodules, tuberculomas, and periapical granulomas.[66,68,69]

Clinical investigations: A thorough patient history and clinical evaluation is key. Biopsy and microbiologic assessment provide the conclusive evidence.

Viral infections

A variety of virus infections can present with lesions in the oral mucosa and gingiva. Hand-foot-and-mouth disease caused by coxsackie viruses is one of those affecting mostly children under 10 years of age and often sweep through childcare units or schools.[70,71]

Clinical findings: Children present with blisters in the mouth, mainly affecting the tongue, buccal mucosa, and the throat. Typical lesions can also be observed on the palms of the hands and around

TABLE 2 Classification of non-plaque-induced gingival diseases and conditions according to Ref. [56].

Genetic/ developmental disorders
- Hereditary gingival fibromatosis

Specific infections
- Bacterial origin
  - Neisseria gonorrhea
  - Treponema pallidum
  - Mycobacterium tuberculosis
  - Streptococcus gingivitis
- Viral origin
  - Coxsackie virus (hand-foot-and-mouth disease)
  - Herpes simplex virus types 1 and 2
  - Varicella zoster virus (chicken pox or shingles affecting nerve V)
  - Molluscum contagiosum
  - Human papilloma virus
    - Squamous cell papilloma
    - Condyloma acuminatum
    - Verruca bulgaris
    - Focal epithelial hyperplasia

Inflammatory and immune conditions
- Hypersensitivity reactions
  - Contact allergy
  - Plasma cell gingivitis
  - Erythema multiforme
- Autoimmune diseases of skin and mucous membranes
  - Pemphigus vulgaris
  - Pemphigoid
  - Lichen planus
  - Lupus erythematosus
- Granulomatous inflammatory conditions (orofacial granulomatosis)
  - Crohn's disease
  - Sarcoidosis

Reactive processes
- Epulides
  - Fibrous epulis
  - Calcifying fibroblastic granuloma
  - Pyogenic granuloma (vascular epulis)
  - Peripheral giant cell granuloma (or central)

Neoplasms
- Premalignant
  - Leukoplakia
  - Erythroplakia
- Malignant
  - Squamous cell carcinoma
  - Leukemia
  - Lymphoma

Endocrine, nutritional, and metabolic diseases
- Vitamin deficiencies
  - Vitamin C (scurvy)

Traumatic lesions
- Physical/mechanical insults
  - Frictional keratosis
  - Mechanically induced gingival ulceration
  - Factitious injury
- Chemical burn
  - Etching
  - Chlorhexidine
  - Acetylsalicylic acid
  - Cocaine
  - Hydrogen
  - Dentifrice detergents
  - Paraformaldehyde or calcium hydroxide
- Thermal insult
  - Burns to gingival mucosa
- Gingival pigmentation
  - Melanoplakia
  - Smoker's melanosis
  - Drug-induced pigmentation
  - Amalgam tattoo

the fingers and toes. Starting with red dots, the lesions develop into vesicles that finally rupture.[54]

Infection with herpes simplex virus types 1 and 2 as well as varicella zoster may pass asymptomatically but may also rarely be associated with gingivostomatitis mostly occurring in infants when the viruses first hits.[72]

Human papilloma virus (HPV): Only very few of the different subtypes can be found in the oral cavity, the squamous cell papilloma and verruca vulgaris are most common types.[73,74] They appear as painless, small, whitish icicle-like or cauliflower-like protrusions.

Primary herpetic gingivostomatitis manifests as painful severe gingivitis with general redness, or ulcerations and in case of stomatitis with edema. Often vesicles are first observed, which rupture and coalesce into fibrin-coated ulcers. Children might be feverish. In adults, recurrent intraoral herpes lesions might be mistaken for aphthous ulcerations.[72]

Clinical investigations: Besides patient history and clinical examination, HSV from lesions can be sampled and tested by polymerase chain reaction. Alternatively, blood can be evaluated for antibody titers against HSV.

Fungal infections

Fungal infections comprise a variety of diseases such as aspergillosis, blastomycosis, candidosis, and histoplasmosis. The most common fungal infection affecting the oral mucosa is caused by *C. albicans*. Infection with *C. albicans* has been associated with a reduced host response like immunodeficiency, reduced salivary flow, smoking, removable prostheses, or treatment with corticosteroids or asthma sprays.[75]

Clinical findings: Signs and symptoms include creamy white lesions mostly on the tongue, inner cheeks, on the palate, gingiva, and tonsils. Different types can be distinguished as pseudomembranous, erythematous, plaque-like type, and nodular type of candidosis. Unlike the pseudomembranous form that can be wiped off, the plaque-like and nodular type are non-scrapable. Some of the lesions take on a cottage cheese-like appearance.[76] Less commonly, they appear as a red area.

Clinical investigations: A thorough patient history and clinical examinations are the basis for identifying the infection. The diagnosis can be accomplished by smear culture or biopsy.[54]

5.1.2 | Inflammatory and immune conditions and lesions

Hypersensitivity reactions and erythema multiforme

Allergic reactions in the oral mucosa are rare. Reactions to restorative materials may bear similarities with oral lichen planus lesion or oral leukoplakia. Dentifrices, mouthwashes, or food ingredients might also give rise to type IV hypersensitivity reactions.

Erythema multiforme is a rare, self-limiting acute immune-inflammatory reaction of the oral mucosa with unknown etiology. It mostly affects young adults.[54] Characteristically, swollen lips are accompanied by heavy crust formation along the vermilion border. Characteristically, at the buccal mucosa and the gingiva rupturing bullae appear leaving extensive ulcers.[54]

Clinical findings: The clinical manifestation of type IV hypersensitivity reactions occur within a timeframe of 48 h after exposure to the allergen. Erythema multiforme displays swollen lips with severe crust formation of the vermilion border and gingival or mucosal bullae that rupture leaving extensive ruptures. Skin lesions are characterized by an iris appearance with a central bulla surrounded by a pale halo and an erythematous zone.[77]

Clinical investigations: Allergy testing with skin patches might be considered.

5.1.3 | Autoimmune diseases

Pemphigus vulgaris

Pemphigus vulgaris (PV) is a rare immunoglobulin G (IgG) -mediated autoimmune disorder that is characterized by intraepithelial blistering in the mouth and on the skin.[78] These blisters are caused by auto-antibodies directed against epithelial desmosomal glycoproteins[79,80] which result in intraepithelial cleavage. The disease develops in middle aged or elderly individuals. The incidence varies between 0.5 and 6.1/100000 in the population. Of note, Israeli and Ashkenazi Jewish women are more often affected from PV than men and other populations.[81]

Clinical findings: Bulla formation are characteristic for the disease that may affect large areas of the skin. Often the disease presents first with oral lesions. Early lesions might bear resemblance with aphthous ulcers; later into the disease, widespread, painful desquamative lesions, erosions, or ulcerations occur. The lesions heal without scarring, but bulla formation is recurrent. Other mucous membranes are involved.

Clinical investigations: Patient history and clinical inspection are mandatory. A positive Nikolsky sign is characteristic for PV, which describes the formation of visible erosion and intraepithelial disruption when applying lateral tension or friction by a finger on the skin.[82] When PV is suspected, patients should be immediately referred to the dermatologist as life-threatening complications can occur. The diagnosis can be confirmed histologically by intraepithelial bulla formation.[83] Blood serum reveals circulating autoantibody titers to desmoglein 1 and 3 that are detectable by enzyme-linked immunosorbent assay mostly later than the initial stage.[83,84]

Pemphigoid

Similarly to PV, pemphigoid is caused by autoantibodies but here toward distinct components of the dermal-epidermal junction. Consequently, the epithelium detaches from the connective tissue. Pemphigoid so far describes eight disorders of which the targets all have been identified.[81] Bullous pemphigoid (BP) is the most common type with an annual incidence of 2.4–21.7 new cases per million population.[85–87] It is mainly considered as a disease of the elderly and is rarely encountered in individuals younger than 50 years. One type of pemphigoid, the mucous membrane pemphigoid (MMP) affects mucous membranes, most commonly the oral mucosa, the ocular mucosa, oropharynx, larynx and the genital region.

Clinical findings: Oral lesions are present in about 30% of the patients with BP and in about 40% with MMP. Oral lesions appear as irregular diffuse ulcers, erosive patches with pseudomembranes, or generalized gingival erythema.

Clinical investigation: Patient history and extra- and intraoral examination might reveal the diagnosis. The ocular mucosal inspection should be inspected. With BP, the Nikolsky sign is mostly negative, while with MMP an induced trauma can elicit blisters and erosion (Nikolsky positive).[88] Biopsy should involve perilesional tissue for histological and immunohistochemical examination that can distinguish the different types of pemphigoid. Circulating antibodies in the blood are not always detected.

Lichen planus

Oral lichen planus (OLP) is a recurrent mucocutaneous autoimmune disease displaying characteristic white lace-like lesions. It is a common disorder with a global prevalence of 1%[89] to up to 2%[90] with a female preponderance. Erosive/ulcerative OLP has been classified as potentially malignant disease. Tongue localization, presence of atrophic-erosive lesions, and alcohol consumption are risk factors for malignant transformation.[91] Six types of OLP have been identified (papular, reticular, plaque-type, erythematous, ulcerative, bullous). Basically, it has been described as an inflammatory reaction against an unidentified antigen in the basal epithelial layer/ within the basement membrane. Approximately 15% of patients with OLP have also cutaneous lesions, 20% also genital lesions.[92]

Clinical findings: OLP most commonly affects the buccal mucosa, tongue, and gingiva (Figure 10). It often shows a bilateral, symmetric distribution. Two or even more types of OLP can occur simultaneously (Figure 11). The reticular type displays characteristic interlacing white lines (i.e., Wickham striae) and often manifests in the posterior buccal areas.[92] The papular type often appears concurrently with the reticular type. The erythematous type is characterized by atrophic, erythematous lesions with radiating striae in the periphery. The erythematous, ulcerative, and bullous types usually present with symptoms that require treatment.[92]

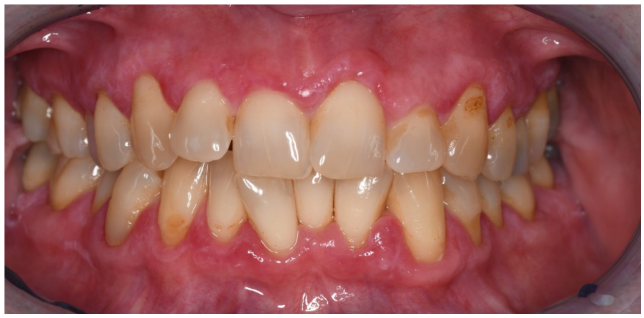

FIGURE 10 Clinical frontal view of a young female patient with generalized oral lichen planus lesions. Courtesy of PD Dr. V. Suter, Department of Oral Surgery and Stomatology, University of Bern, Bern, Switzerland.

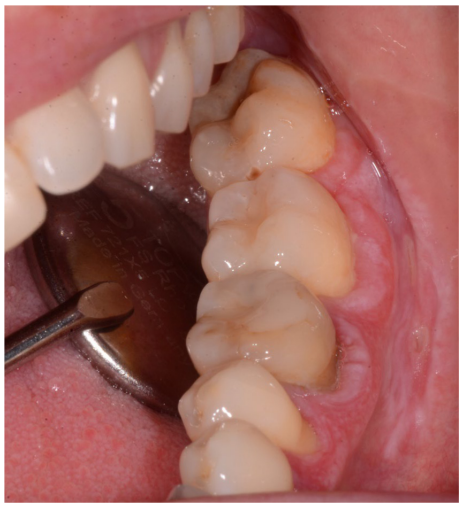

FIGURE 11 Combined reticular and ulcerative oral lichen planus lesions in the posterior mandible of a 40-year-old female patient. Courtesy of PD Dr. V. Suter, Department of Oral Surgery and Stomatology, University of Bern, Bern, Switzerland.

Clinical investigations: Patient history and clinical inspection is of utmost importance. The diagnosis is based on the presence of bilateral papular-, reticular-type lesions. Histopathological evaluation reveals hyperkeratosis, degenerative changes of basal cells, and subepithelial band-like accumulation of lymphocytes and macrophages characteristic for a type IV hypersensitivity reaction.[92] Given the premalignant characteristics of certain OLPs, regular check-ups are recommended.

Lupus erythematosus

Lupus erythematosus (LE) is a group of autoimmune diseases that develop autoantibodies against various cellular components including nuclear and membrane components. Two forms are known: discoid LP (DLE) and systemic LP (SLE), which may affect several organs. The annual incidence for SLE varies between 3.7 and 49 per 100000 persons.[93,94] For DLE, annual incidence estimates of about 0.5–6.5 per 100000 individuals have been published.[95] Both forms are more common in women than men. DSE is chronic, although mostly shows a mild form affecting the mucous membranes including the gingiva and oral mucosa.

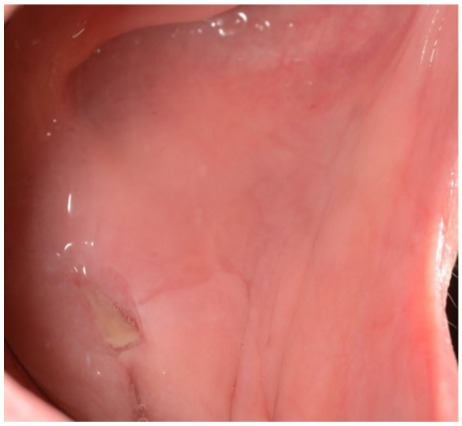

FIGURE 12 Squamous cell carcinoma in the retromolar region of a 90-year-old patient.

Clinical findings: The typical lesion has a central atrophic area with white dots surrounded by irradiating fine white striae. Characteristic for DLE is a Bordeaux-colored, butterfly-shaped rash on the bridge of the nose and the cheek consisting of photosensitive, scaly macules. Oral lesions can also ulcerate or resemble OLP lesions.

Clinical investigations: Patient history and clinical extra- and intraoral inspection are the first pillars of the diagnosis. Further, histopathological evaluation shows characteristic changes, that is, hyperkeratosis, keratin plugging and variation in epithelial thickness, liquefaction of basal cells, and increased width of the basement membrane. Immunohistochemistry often reveals immunoglobulins, C3, and fibrin along the basement membrane. Blood test may reveal lower numbers of erythrocytes, further antinuclear antibodies (ANA) might be detected. Diagnosis of SLE might be challenging given the heterogeneity of the clinical features.

Reactive processes

Epulides describe very broadly exophytic processes originating from the gingiva. Usually, they are not accompanied with symptoms. Several types can be distinguished, including the fibrous epulis, the calcifying fibroblastic granuloma, the pyogenic granuloma (i.e., vascular epulis), and the peripheral giant cell granuloma.[54]

Clinical findings: The fibrous epulis displays a smooth pink surface, the calcifying fibroblastic granuloma can reach larger sizes, although usually smaller than 1.5 cm, and can, if occurring interdentally, separate adjacent teeth. The pyogenic granuloma often develops during pregnancy. The peripheral giant cell granuloma is the most common reactive lesion and appears as swollen, sessile or pedunculated, at times ulcerated process.[54]

Neoplasms

Squamous cell carcinomas represent about 90% of intraoral carcinomas with a predilection for the posterior mandible[96] (Figure 12). It is important to note that oral lesions can also be manifestations of leukemias and non-Hodgkin lymphomas.

Clinical findings: The primary stage can be an ulcer or small nodules that might have an innocent appearance.

Clinical investigations: Biopsy is needed for diagnosis. Immediate referral is of utmost importance because, when detected early, oral squamous cell carcinomas can be cured in 89%–90% of cases, whereas later into the disease at stage 3 and 4, the survival rate decreases to 20%.[54]

Traumatic lesions

Traumatic lesions of the gingiva can be found after physical/mechanical insults and may be induced by a traumatic tooth brushing technique or can be due to chemical insults including the use of chlorhexidine, acetylsalicylic acid, cocaine, hydrogen peroxide. Burns caused by very hot food can further cause lesions.

Clinical findings and investigation: Patient history and clinical examination are important for the diagnosis.

5.2 | Periodontitis as a manifestation of systemic diseases

Several systemic diseases and medication have a severe impact on the periodontal tissues and may cause periodontal attachment loss and bone loss or aggravate periodontal tissue loss.[97,98]

Some of these diseases are innate, others are acquired later on in life. Disorders that impair the immune response predispose these individuals to infections and also to a higher prevalence and severity of periodontal disease that depending on the severity of the impairment might already set in during adolescence. Genetic disorders derive from gene mutations or chromosome aberrations. As individuals with genetic disorders most often present with other systemic conditions, the genetic background is in most cases known before individuals seek dental care/treatment. Here, only the most common disorders and conditions are discussed, while the full classification from the 2017 World Workshop is listed in Table 3.

5.2.1 | Systemic disorders with major impact on the loss of periodontal tissues by influencing periodontal inflammation

Genetic disorders: Diseases affecting the immune response

Down syndrome. Despite significant improvements in prenatal screening tests that are now able to detect chromosomal material from the fetus circulating in the maternal blood, Down syndrome continues to be the most common disorder. In the United States,

TABLE 3 Classification of diseases and conditions affecting the periodontal tissue according to References[97,98].

Systemic disorders that have a major impact on the loss of periodontal tissue by influencing periodontal inflammation:

Genetic disorders

- Diseases associated with immunologic disorders
  - Down syndrome
  - Leukocyte adhesion deficiency syndromes
  - Papillon-Lefèvre syndrome
  - Haim-Munk syndrome
  - Chediak-Higashi syndrome
  - Severe neutropenia
    - Congenital neutropenia
    - Cyclic neutropenia
  - Primary immunodeficiency diseases
    - Chronic granulomatous disease
    - Hyperimmunoglobulin E syndromes
  - Cohen syndrome
- Diseases affecting the oral mucosa and gingival tissue
  - Epidermolysis bullosa
    - Dystrophic epidermolysis bullosa
    - Kindler syndrome
  - Plasminogen deficiency
- Diseases affecting connective tissues
  - Ehlers-Danlos syndrome (IV, VIII)
  - Angioedema (C1-inhibitor deficiency)
  - Systemic lupus erythematosus
- Metabolic and endocrine disorders
  - Glycogen storage disease
  - Gaucher disease
  - Hypophosphatasia
  - Hypophosphatemic rickets
  - Hajdu-Cheney syndrome
  - Diabetes mellitus
  - Obesity
  - Osteoporosis

Acquired immunodeficiency diseases

- Acquired neutropenia
- HIV infection

Inflammatory diseases

- Epidermolysis bullosa acquisita
- Inflammatory bowel disease
- Arthritis (rheumatoid arthritis, osteoarthritis)

Other systemic disorders that influence the pathogenesis of periodontal disease:

- Emotional stress
- Smoking
- Medications

Systemic diseases that can result in loss of periodontal tissue irrespective of periodontitis:

- Neoplasms
  - Primary neoplastic diseases of periodontal tissue
    - Oral squamous cell carcinoma
    - Odontogenic tumors
    - Other primary neoplasms of periodontal tissue
  - Secondary metastatic neoplasms of periodontal tissue
- Other disorders that may affect periodontal tissue
  - Granulomatosis with polyangiitis
  - Langerhans cell histiocytosis
  - Giant cell granulomas
  - Hyperparathyroidism
  - Systemic sclerosis (scleroderma)
  - Vanishing bone disease (Gorham-Stout syndrome)

according to the Centers for Disease Control and Prevention (CDC), each year about 6000 babies are born with Down syndrome (DS) that is caused by a chromosome alteration resulting in three copies of all or part of chromosome 21. At birth, DS babies present with certain physical traits such as low muscle tone, a single deep crease across the palm of the hand, and an upward slant to the eyes, as well as pathological characteristics that often include congenital heart disease, gastrointestinal disease, mental retardation, and other conditions like leukemia, epilepsy, and autoimmune diseases. A karyotype confirms the diagnosis. Individuals are prone to a higher susceptibility to infections which are caused by impaired phagocytotic function of polymorphonuclear leukocytes, agammaglobulinemia,[99] alterations in T- and B-cell subpopulations,[100] high levels of tumor necrosis factor (TNF)-α and interferon (IFN)γ,[101] to increased immunoactivity, and altered ratios of $CD8^+$-, $CD4^+$-, and $CD56^+$ natural killer (NK) cells.[102]

Clinical findings: Down syndrome is characterized by mid-facial growth deficiency and Class III malocclusion. A generalized orofacial muscles hypotonia results in poor oral muscle seal, poor suck, and poor tongue control.[103] The lower lip is thick and everted, the mouth angles are pulled downward, and the mouth stays mostly often due to the relatively large tongue. In children with DS, frequent orolabial lesions occur, such as fissured tongue (78%), lip fissures (64%), angular cheilitis (38%), and cheilitis (14%).[104] Microdontia of permanent teeth, altered crown morphology, taurodontism, hypodontia and supernumerary teeth, delayed and asymmetric eruption are common characteristics.[103] The mucosal lining of the oral cavity is generally thin due to the reduced salivary flow. DS individuals generally present with poor oral hygiene which together with a compromised immune response manifests as marginal gingival inflammation. DS individuals show increased prevalence and severity of periodontal diseases which often sets in by mid to late teen years.[105–108]

Clinical investigations: Dental treatment should follow an interdisciplinary approach. A thorough clinical and radiographic examination should be preceded by consultation of treating physicians and cardiologists as often congenital heart malformations occur and a high percentage develop mitral valve prolapse later on that might not have been discovered yet. A thorough medical history and a medical check-up including blood testing of immune cells and glucose levels cannot be over-emphasized.

Leukocyte adhesion deficiency. Leukocyte adhesion deficiency (LAD) is a rare syndrome affecting 1 out of 100000 births. It is characterized by an autosomal recessive mutation on the CD18 subunit of β_2 integrins or other adhesion molecules. Three types are known (LAD-I, II, and III), whereby LAD-I is the most common one. Given the lack of adhering molecules, neutrophils cannot adhere to endothelial cells and extravasate to sites of infection or inflammation. Infants with LAD present with a delayed detachment of the umbilical cord stump as one of the first signs, then develop severe bacterial infections and inflammations in particular affecting the skin, mucous membranes, lungs, and gingival tissues and usually lose their primary dentition.

Clinical findings: LAD-1 individuals present with severe forms of periodontal disease already during adolescence. Although tissues are severely inflamed, LAD infections characteristically lack pus formation. LAD-I periodontitis is triggered by microbial biofilms and caused by deficient neutrophil surveillance and then by dysregulated IL-23/IL-17 cytokine levels.[109] Intriguingly, the LAD-I microbiome displays unique characteristics compared to healthy or periodontitis patients.

Clinical investigations: While the microbiome of periodontitis patients exhibits an increased diversity and richness in subgingival species in particular at inflamed sites, LAD-I periodontitis is characterized by an increased bacterial load, but a decreased diversity of species and a complete depletion of numerous bacterial species detected in health, including *Actinomyces* or *Streptococci*.[110,111] Patients with moderate deficiency are diagnosed later in life. Although they may have fewer severe infections when compared to severe forms of LAD, they present with leukocytosis, delayed wound healing, and moderate periodontal disease. The diagnosis is based on clinical evaluation, detailed patient history, and confirmed by a high white cell count and finally molecular genetic testing.

Papillon-Lefèvre syndrome. Papillon-Lefèvre syndrome (PLS) is an autosomal recessive inherited disorder that presents with dry scaly patches at the palm of hands and feet as well as a severe form of early-onset periodontitis affecting both primary and permanent teeth.[112] The underlying mechanism is the deficiency of cathepsin C that results in a lack of serine protease activity and a dysregulated host response.[113,114] The incidence lies around 1–4 per million. The pathobiology of the disease was recently shown to be due to relentless recruitment of hyper-responsive neutrophils to periodontal tissues following failed clearance of pathogens.[114] PLS becomes evident by 2–3 years of age when deciduous teeth present with periodontal infections leading to premature shedding of the primary teeth. Some of the PLS individuals are susceptible to other infections than periodontitis.[115]

Clinical findings: Individuals with PLS present with two cardinal features, namely palmoplantar keratosis and rapid periodontal destruction affecting both dentitions.

Clinical investigations: Patient history and clinical inspection including palms of hands and/or feet. Diagnostic tests involve genetic test for mutations of cathepsin C gene on chromosome 11q14. Further, a test is available for testing cathepsin C deficiency in the urine.

Severe neutropenia. Congenital neutropenia (e.g., Kostmann syndrome) comprises a group of hematological diseases that result in impaired maturation of neutrophil granulocytes. Individuals with congenital neutropenia commonly suffer from recurrent infections beginning by 2–3 months after birth. Later on, periodontal inflammation and tissue destruction are common (Figure 13).[116] The Kostmann syndrome occurs in 3–10 individuals out of 1 million.[114] Mutations in the *ELANE* genes encoding for neutrophil elastase seem to be crucially involved in the pathogenesis of periodontitis in patients with congenital neutropenia.[117,118] Neutropenia can further be the result of cancer treatment.

Clinical findings: Individuals with severe forms of neutropenia struggle with recurrent infections. Periodontal inflammation and tissue destruction are common in these individuals.

Clinical investigations: Patient history and clinical diagnosis in most cases depict a clear picture of the disease. The initial diagnosis is based on blood examination and neutrophil count as well as genetic testing for mutations in *ELANE*.

Diseases affecting the gingival tissue, mucosa, and connective tissue

Mutations in genes relevant for the functioning of the basement membrane (e.g., Kindler syndrome) or in collagen chains like in dystrophic epidermolysis bullosa or Ehlers-Danlos syndrome usually present with recurrent blister formation on the skin, the oral mucosa, and with severe loss of keratinized tissue and of periodontal tissues as clinical findings.[119–121]

Clinical investigations: Genetic testing confirms the diagnosis.

Metabolic or endocrine disorders

Diabetes mellitus (DM) refers to a group of disorders affecting the insulin-glucose system resulting in chronic hyperglycemia. It is one of the most important global health threats of the 21th century with significantly growing numbers over the past 20 years. According to the World Health Organizataion (WHO) an estimated 422 million people globally suffer from DM[122] mainly type II. An insulin-dependent (type I) (Figure 14) and a non-insulin-dependent (type II)

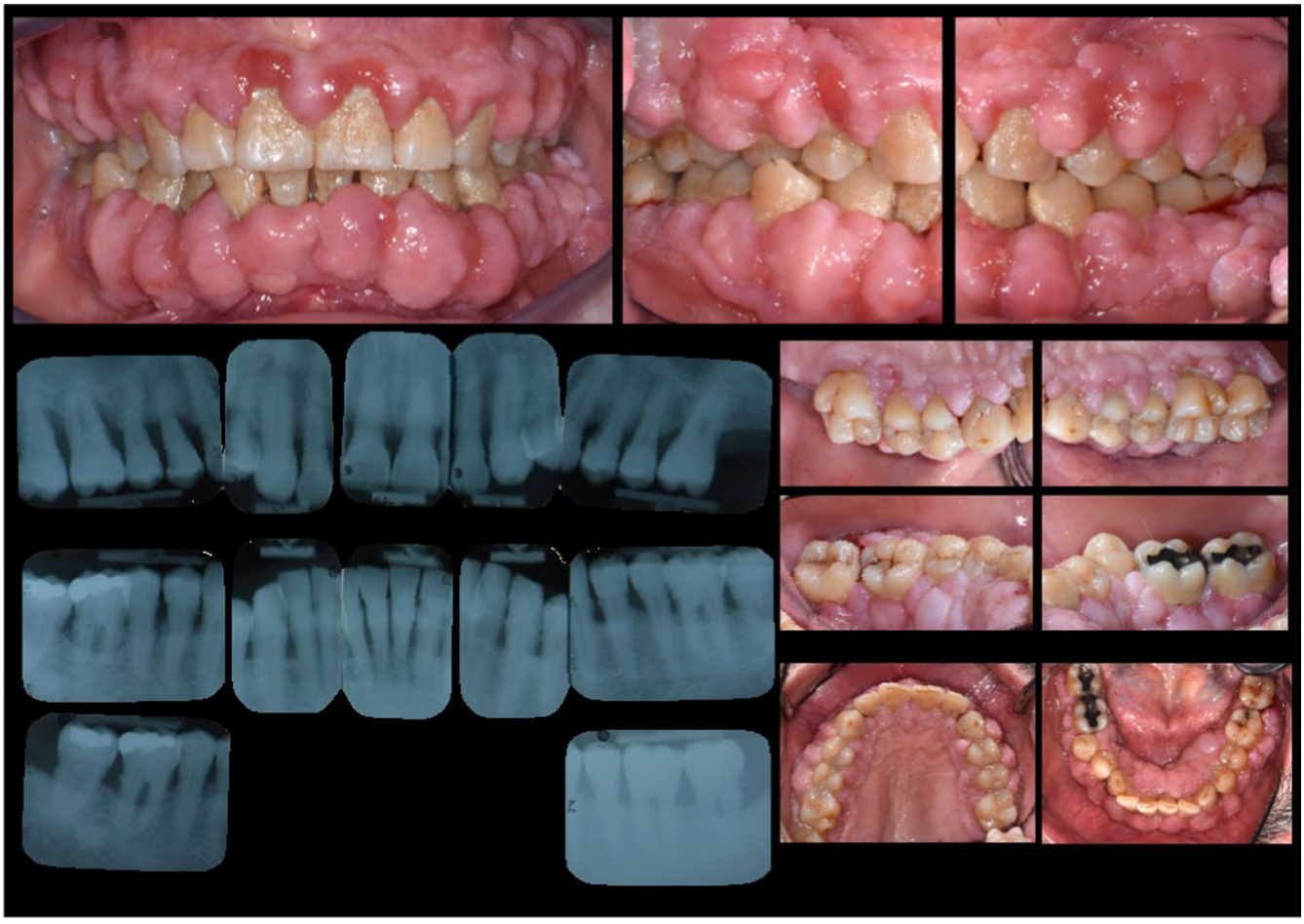

FIGURE 13 Periodontal disease and massive gingival hyperplasia in a patient diagnosed with acquired neutropenia, polyneuropathy, Cushing-syndrome, glomerulonephritis, and hypertensive heart valve disease. The 58-year-old patient took immunosuppressants and calcium antagonists. Periodontal therapy was performed after consultation with the hematologist.

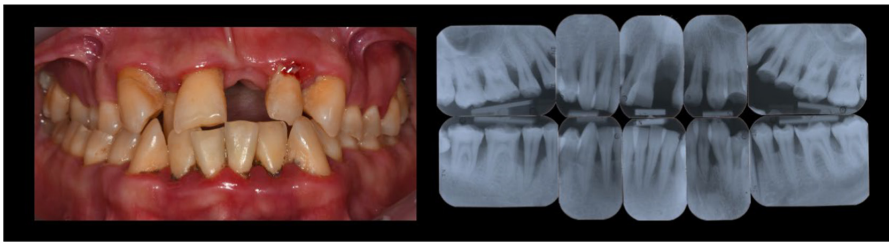

FIGURE 14 Clinical and radiographic overviews of a 28-year-old patient with type I diabetes mellitus and severe periodontitis.

one can be distinguished. Increasing protein glycation and accumulation of advanced glycation end (AGE) products activate numerous intracellular pathways via binding to transmembrane receptors (RAGE) leading to development of DM sequelae over time[123] including retinopathy, nephropathy, or atherosclerosis.

It is well-established that DM type II and in particular when it is uncontrolled, is a considerable risk factor for periodontitis,[124,125] and, vice versa, periodontitis can exacerbate the diabetic development.[126,127]

Clinical findings: A thorough patient history and clinical history are important. While in type I DM, symptoms occur quickly within days or weeks, in type II DM symptoms such as fatigue, numbness, pruritus, drowsiness, increased thirst, frequent urination, and depression often slowly develop or might be veiled by other conditions like aging or being overweight. Intraorally, no hyperglycemia-associated lesions or periodontitis patterns are reported. Individuals with DM have a higher prevalence and severity of periodontitis. Poor glycemic control was further associated with symptoms of xerostomia, burning mouth, coated fissured tongue, oral candidiasis, increased caries activity, and delayed wound healing.[128]

Clinical investigations: A thorough patient history and clinical examination are important. Patients with diabetes or diabetes-like symptoms or, in general, being overweight should be sent to a physician for blood testing (i.e., assessment of fasting plasma glucose level). Glycosylated hemoglobin (HbA1c) should be monitored every 3 months since the lifespan of erythrocytes is about 120 days. The percentage of HbA1c mirrors the glucose level over the last 3 months; it is around 5% in healthy individuals and should not exceed 7.0%–7.5% despite DM.[129]

Other systemic disorders influencing the pathogenesis of periodontal diseases

Medications. Some medications severely impair the host's immune response such as certain cytotoxic chemotherapeutics, others again have an impact about gingival tissue resulting in gingiva hyperplasia or synonymously called gingival overgrowth (Figure 13). Drug-induced gingival overgrowth is a frequent adverse reaction to a certain category of immunosuppressants (ciclosporin), anticonvulsants (Dilantin's e.g., phenytoin), and calcium channel blockers (e.g., nifedipine).[130]

Clinical findings: More or less prominent gingival enlargement is obvious affecting mostly the frontal region. In severe cases, gingival hyperplasia might cover nearly completely the clinical crowns and severely impair oral hygiene (Figure 13).

Clinical investigations: A thorough patient history reveals the underlying cause.

6 | CONCLUSIONS

- Discrimination between periodontal health or disease should form the basis for a pretherapeutic prognosis and a comprehensive treatment plan.
- Assessment of clinical and radiographic parameters prior to therapy and during long-term supportive care is of paramount importance.
- Clinical and radiographic diagnostic parameters should be assessed at the patient, tooth and site level.
- Continuous monitoring of periodontal conditions following each therapeutic step should guide dental professionals on the need for additional treatment measures.
- Cost–benefit aspects and added values of new diagnostic technologies should be carefully evaluated.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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