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PERI-IMPLANTITIS (I DARBY, SECTION EDITOR)

Insights into the Clinical Diagnosis of Peri-implantitis: to Probe or Not to Probe

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Abstract

Purpose of Review The present review aimed at assessing the primary and secondary diagnostic tools currently used to monitor peri-implant conditions.

Recent Findings There has been much debate on the diagnostic accuracy of clinical parameters in monitoring peri-implant conditions. Given the association between pocket depth measured around teeth and implants and the extent of microbial plaque biofilm deposits, it seems plausible for probing pocket depth to be indicative of disease progression or stability. Moreover, understanding the inflammatory nature of peri-implantitis, it seems reasonable to advocate that bleeding, erythema, tumour and suppuration are indicators of pathology. However, cautiousness must be exercised when interpreting clinical findings, since the morphology of peri-implant tissues differ significantly from the periodontal structures.

Summary The routine clinical assessment of dental implants, including probing and visual examination, may lead to the accurate diagnosis of peri-implant disorders. Nevertheless, the definitive diagnosis should be based on agreement with progressive radiographic bone loss. In fact, primary diagnostic tools seem to be highly specific for monitoring peri-implant conditions, while their sensitivity is lower compared with their use in monitoring periodontal stability.

Keywords Peri-implantitis · Periodontitis · Tooth mobility · Dental implants · Dental prosthesis · Endosseous implantation

Introduction

Neglect of the biological complications of peri-implantitis has resulted in part from vague understanding of the disorder, and scarce consensus on case definition. Indeed, several definitions have been proposed in the literature, led mainly by empirical decisions. Levignac described peri-implantitis as an infectious condition of the peri-implant tissues [1]. Two decades later, Mombelli et al. compared peri-implantitis with chronic periodontitis in that both are driven by pathogenic bacteria [2]. Posteriorly, the American Academy of Periodontology and the European Federation of Periodontology proposed different definitions. The European Workshop on Periodontology agreed in 2011 that the case definition for peri-implantitis should include the following criteria: changes in crestal bone level and the presence of bleeding on probing and/or suppuration, with or without concomitant deepening of peri-implant probing pockets [3]. One year later, Sanz and Chapple, on behalf of Working Group 4 of the VIII European Workshop on Periodontology, stated that 2 mm could be used as the radiographic threshold to distinguish between physiological and pathological peri-implant bone loss [4]. The Academy Report of the American Academy of Periodontology further reiterated that peri-implantitis is an inflammatory condition

This article is part of the Topical Collection on *Peri-implantitis*

One-sentence summary: Probing can lead to accurate diagnosis of peri-implantitis.

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Table 1 Clinical characteristics of peri-implantitis according to the case definition employed

Author (year)	Study design	Sample size (patients/ implants)	Case definition of peri-implantitis					
			Clinical parameters				Radiographic parameters	
			BOP	SUP*	PPD > 3 mm	PPD > 5 mm	Progressive bone loss	Threshold
Canullo et al. (2015) [6]	Cross-sectional	56/125	x	x	x		> 3 mm	
Casado et al. (2013) [7]	Cross-sectional	215/754	x	x			≥ 1 mm	
Cecchinato et al. (2013) [8]	Retrospective cohort	133/407	x	x	x		> 0.5 mm	
Derks et al. (2016) [9]	Retrospective cohort	588/225	x	x			> 0.5 mm	
Dierens et al. (2012) [10]	Retrospective cohort	50/59	x	x				≥ 3 threads
Fischer et al. (2012) [11]	Prospective cohort	23/137	x	x				> 4 mm
French et al. (2019) [12]	Retrospective cohort	2060/4591	x	x				≥ 1 mm
Gotfredsen (2012) [13]	Prospective cohort	19/19	x	x				> 2 mm
Karoussis et al. (2003) [14]	Prospective cohort	53/112	x	x			> 0.5 mm	
Marrone et al. (2013) [15]	Cross-sectional	103/266	x	x	x			> 2 mm
Maximo et al. (2008) [16]	Prospective case series	113/374	x	x	x			> 3 threads
Mir-Mari et al. (2012) [17]	Cross-sectional	245/964	x	x				≥ 2 threads
Monje et al. (2018) [18]	Cross-sectional	141/262	x	x		x		≥ 2 mm
Rinke et al. (2015) [19]	Retrospective cohort	65/112	x	x		x		≥ 3.5 mm
Rodrigo et al. (2018) [20]	Cross-sectional	272/474	x	x				≥ 2 mm
Ross-Jansaker et al. (2006) [21]	Retrospective cohort	218/999	x	x			≥ 3 threads	
Rutar et al. (2001) [22]	Retrospective cohort	45/64	x	x	x		> 0.5 mm	
Simonis et al. (2010) [23]	Retrospective case series	55/131	x	x	x			≥ 2.5 mm (≥ 3 threads)

*Simultaneous or not to BOP

BOP bleeding on probing, *SUP* suppuration, *PPD* probing pocket depth

that leads to soft and hard tissue breakdown and courses with clinical signs of inflammation [5]. Table 1 shows the clinical characteristics of peri-implantitis according to the case definition used.

More recently, the case definition proposed by Workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions underscored the need to monitor radiographic bone loss on a longitudinal basis in order to validate the hypothesis that bone loss occurs as a consequence of disease [24••]. Accordingly, a radiographic examination at a given timepoint should be compared with the baseline radiographic bone level (12 months after prosthesis delivery). Alternatively, the following criteria can be used for the diagnosis of implants in the absence of baseline data:

- Presence of bleeding (BOP) and/or suppuration (SUP) on gentle probing (0.15 Ncm)
- Probing pocket depths (PPD) of ≥ 6 mm
- Bone levels ≥ 3 mm apical to the most coronal portion of the intraosseous part of the implant.

Contextualizing the case definition of peri-implantitis on a historical basis and considering the significant inconsistencies of the parameters used for its diagnosis, the wide prevalence ranges of the disorder reported in the literature come as no surprise.

Epidemiology of Peri-implantitis

Evidence on the worrisome prevalence of peri-implantitis has been published in relation to different environments and geographical settings. The prevalence varies extensively according to the case definition adopted. For instance, two meta-analyses pooling data from epidemiological studies on peri-implantitis showed that the prevalence at patient level ranges from 1 to 47% and from 12.5 to 36.5% [25, 26]. This was illustrated in a study conducted using the data from the Swedish Social Insurance Agency. Derks et al. demonstrated that the percentage bone loss adopted for the case definition of peri-implantitis dictates the frequency of the disease. As such, the prevalence was 45%, 26.9%, 14.5%, 10.1%, and 5.9% for peri-implant bone loss > 0.5 mm, > 1 mm, > 2 mm, > 3 mm, and > 4 mm, respectively [9]. Similarly, French et al. compared "strict" BOP criteria versus" relaxed" BOP criteria which ignored light single point bleeding after 6 to 7 years. They reported the prevalence of mucositis to be 38.6% versus 14.2% when using "strict" versus "relaxed" criteria, respectively, and the prevalence of peri-implantitis was 4.7% and 3.6% when using "strict" versus "relaxed" criteria, respectively [12].

On standardizing the case definition of peri-implantitis, however, the disease does not seem to pose a burden as evidenced by previous epidemiological data. Lee et al. demonstrated that the prevalence at patient level was 19.8% [27]. More recently, Rakic et al. showed the prevalence of peri-implantitis to be 12.8% at patient level when including reports adhered to the case definition proposed by Working Group 4 of the VIII European Workshop on Periodontology [28]. In this sense, it is important to note that there is an agreement in the epidemiological reports concerning the site-specificity pattern of the disease. In other words, the prevalence of peri-implantitis at patient level is generally higher compared with the prevalence at implant level, which tends to be approximately two times greater.

Onset and Progression of Peri-implantitis

Peri-implantitis, like periodontitis, is an irreversible condition that courses with peri-implant bone loss [29]. Limited evidence has been reported on the onset and progression of the disease. Nevertheless, recent findings seem to indicate that peri-implantitis manifests about 3 years or later after implant placement [30]. Moreover, the progression of peri-implantitis has been shown to follow an accelerating non-linear pattern. This means that early and accurate diagnosis is crucial for predictable management during the reversible stages of the disease (i.e., mucositis). Hence, routine monitoring led by the reporting of clinical parameters is essential for preventing disease progression and for efficient disease arrestment [31].

Primary Diagnostic Tools

Probing Pocket Depth

Residual pockets favor the progression of periodontal breakdown. In fact, PPD ≥ 6 mm after active periodontal therapy has been cited as a risk factor for tooth loss. Similarly, peri-implant probing should be considered essential for monitoring the peri-implant conditions. Nonetheless, some clinicians suggest that PPD and BOP measurements are poor indicators of peri-implant tissue conditions, and that disturbance of the soft tissue barrier at implants may instead induce inflammation and bone resorption. Moreover, over-diagnosis and overtreatment related to poor indices may result in iatrogenic damage to the implant-tissue interface [32].

In this sense, it is worth mentioning that several shortcomings exist in probing. For instance, PPD relies on direction, angulation, and force, which in turn, might be altered by the prosthesis design (Fig. 1). It has also been suggested that probe force and dimensions should be standardized to improve the diagnostic potential, with the target probe tip penetration being 120 Ncm^2 in order to minimize false positive BOP results [33]. This is achieved by a using a 0.4 mm tip (Marquis) at 15 N, a 0.5 mm tip (UNC) at 23 N, or a 0.6 mm tip (plastic) at 34 N. Furthermore, a recent study has reported that most clinicians probe 2–3 times higher than 120 Ncm^2, thereby increasing the risk for high false positive BOP results [34]. Likewise, probe tip penetration may mislead accurate probing. Knowing the weak hemidesmosome attachment to the implant/abutment surface, light probing is therefore suggested (0.15 N), although this critical aspect has been overlooked in most the studies and may account for the lack of diagnostic value and inter-examiner agreement in earlier publications. It is also worth mentioning that the presence of keratinized mucosa has been associated with lower levels of prostaglandin E2 [35••]. This fact might explain the positive effect of keratinized mucosa on the development and resolution of experimental mucositis in humans [36].

There are significant differences in PPD around teeth and implants, depending on the condition involved. In healthy individuals, Eriksson and Lindhe found the resistance of the gingiva to probing to be greater than that of the peri-implant mucosa, and probe penetration consequently proved greater at implants than at teeth [37]. Lang et al. showed PPD to be an accurate diagnostic tool for monitoring peri-implant inflammation. In fact, it was shown that the probes were able to identify the connective tissue adhesion level in the healthy group, with a mean error of − 0.05 mm (mean histological PPD: 1.75 mm), versus − 0.02 mm in the mucositis group (mean histological PPD: 1.62 mm). Probe penetration increased with the degree of inflammation, and in the peri-implantitis group, the probe exceeded the connective tissue level by an average of 0.52 mm (mean histological PPD: 3.8 mm) [38]. Schøu et al. found that even mild marginal inflammation was associated to deeper probe penetration around implants in comparison with teeth. Interestingly, it was shown in *Macaca fascicularis* that the mean difference on probing implants with mucositis and peri-implantitis was only 0.5 mm, while the range on probing teeth with gingivitis and periodontitis was 0.5–1.5 mm [39]. A canine study has recently shown that PPD in fact increases gradually as the bone is lost, as a response to ligature-induce peri-implantitis progression [40]. Table 2 presents a summary of tip penetration according to the soft and hard tissue levels at teeth and implant sites.

Recently, clinical studies have validated previous preclinical investigations. A matched case-control study noted that the accurate diagnosis of peri-implantitis does not rely only on isolated parameters, but on a combination of parameters. Nevertheless, it was shown that PPD might accurately discern among peri-implant conditions [18••]. Ramanauskaite et al. demonstrated that peri-implantitis patients exhibited

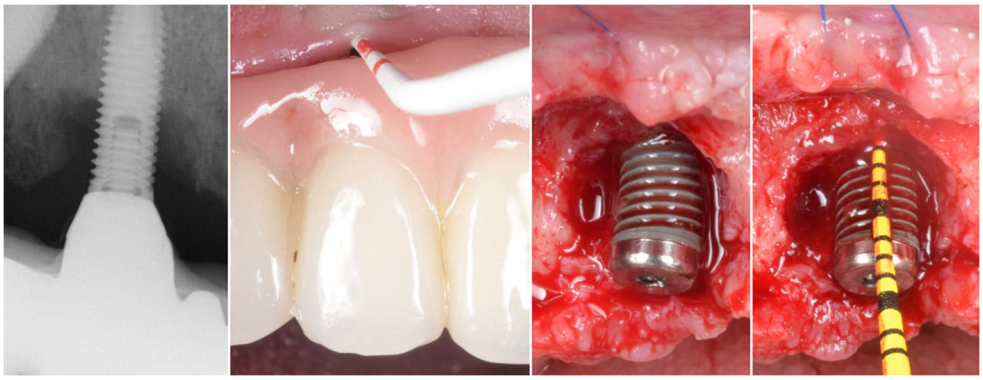

Fig. 1 Probing pocket depth can lead to the accurate diagnosis of peri-implantitis, as it is often associated to the extent of bone loss. Nevertheless, inappropriate prosthesis designs may hinder preciseness in probing

significantly higher mean PPD values (4.46 mm) when compared with the peri-implant mucositis group (2.70 mm). This evidences the accuracy of PPD in monitoring peri-implant conditions.

Bleeding on Probing

The sensitivity/specificity of BOP around teeth and around implants has been on the subject of debate. Around natural teeth, BOP was shown to be accurate for attachment losses > 2 mm (87%). On the other hand, while sensitivity was shown to be low (29%), specificity was high (88%) [41]. In fact, several aforementioned factors such as probing force should be considered when probing, in order to minimize false negative results. Knowing the morphology of the peri-implant tissues, bleeding on dental implants is an even more complex issue. In a canine study, Ericsson and Lindhe reported that deeper probe penetration with BOP positivity does not necessarily reflect disease, since it was displayed around healthy implants as well [37]. In the clinical setting, this is reflected by studies that report high rates of BOP but low rates of bone loss. For example, Cecchinato et al. reported implants with 80% BOP but only 14% developed bone loss [42]. On the other hand, Lang et al. did not notice BOP around healthy implants, while BOP was present in mucositis (67%) and peri-implantitis sites (91%) [38]. Merli et al. in turn found the odds ratio (OR) of BOP at a site to increase by 1.81 for each 1 mm increment in PPD [43]. Fransson et al. showed BOP to occur in over 90% of the implants with no progressive bone loss [44]. Monje et al. found BOP to be sensitive in diagnosing peri-implant mucositis compared with healthy conditions (OR = 2.13) and in diagnosing peri-implantitis compared with healthy conditions (OR = 2.32) [18]. A recent systematic review has concluded that BOP positive implants have a 24.1% chance of being diagnosed with peri-implantitis. Hence, findings from these studies warrant the accuracy of BOP in monitoring peri-implant conditions, but alert to the considerable false-positive rate of BOP in diagnosing peri-implantitis [45] (Fig. 2).

Since false-positive BOP remains an issue, it is critical for probe tip force and dimension to be defined and standardized towards the target of 120 Ncm^2 [33] and the non-dichotomous index used. Implants are potentially more prone to false positive BOP [33], so dichotomous scales limit the diagnostic potential. Indeed, there is presently poor agreement using existing indices for peri-implantitis, with only 52% of all examiners showing agreement in peri-implantitis diagnosis [46]. The problem in the literature is that that historical data on peri-implantitis were based on dichotomous scoring (BOP+ versus BOP-). For example, of the 23 studies included in the EAO 2012 consensus on peri-implantitis, 12 used binary BOP and/or suppuration scoring, while 9 studies used binary BOP with no reference to SUP, and one study made no reference to either BOP or SUP [47].

Given the fact that BOP might be the result of trauma, implant specific indices have been proposed as a modification of prior dental indices in order to compensate the inherent limitations of dichotomic scales. For instance, the modified sulcular bleeding index (mSBI) has been widely used, as profuseness and extensiveness are considered in the scoring system [2] (Table 3). The peri-implant mucosal tissue index further describes the inflammatory condition of the mucosa [48]

Table 2 Probe tip penetration at teeth and implant sites according to the soft and hard tissue condition

Condition	Periodontal tissue	Peri-implant tissue
Healthy	1/3 apical LJE	1/3 apical 1/3 apical EB-1/3 coronal CT
Gingivitis/mucositis	1/3 apical LJE-1/3 coronal CT	2/3 apical CT
Periodontitis/peri-implantitis	1/3 coronal CT	1/3 apical CT-bone

LJE long-junctional epithelium, *CT* connective tissue, *EB* epithelial barrier

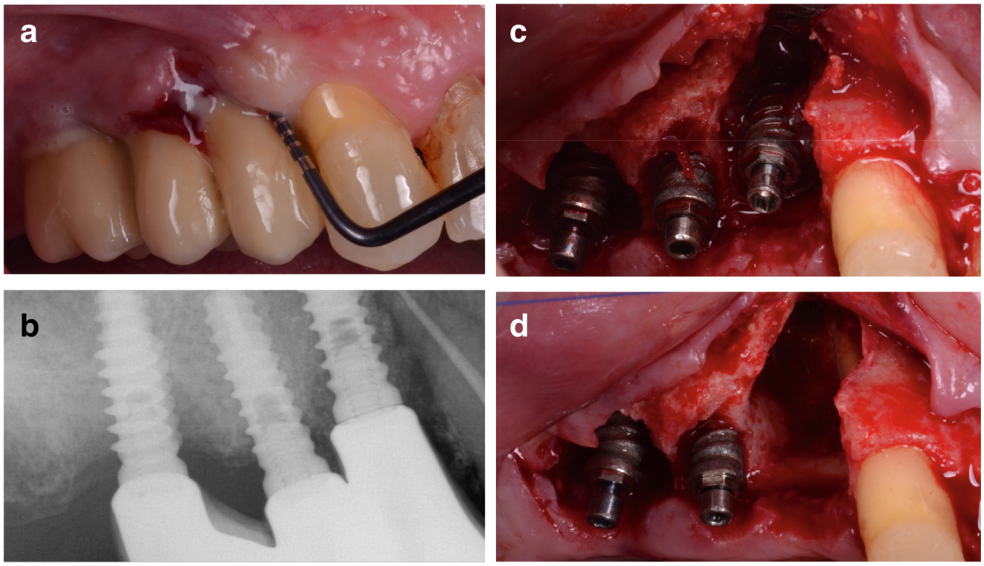

Fig. 2 Profuse bleeding is compatible with moderate to advanced peri-implantitis lesions

(Table 4). Though incorporating graded bleeding is an improvement over dichotomous bleeding scores, some scales do not use a controlled probe force and utilize visual color changes which can be complicated by gingival coloring from the underlying titanium of the abutment or implant. As part of the 2017 Word Workshop "case definitions and diagnostic considerations" review paper, it was highlighted that for the case definition of mucositis and peri-implantitis, visible inflammation and profuse (line or drop) bleeding should be present, whereas isolated bleeding spots secondary to non-plaque induced trauma should be excluded [49]. Furthermore, SUP—an important parameter within any given medical science—has been neglected in these historical indexes. Failure to incorporate suppuration in combination or not with BOP into implant specific indices risks reporting false negative results in the most advanced cases of the disease. Recently, the implant mucosal index (IMI) has been proposed to overcome drawbacks associated to the sensitivity of BOP, using controlled probe force (17-g automated Florida Probe or CP-12 Hu-Friedy manual probe), and a tip dimension of 0.45 mm, which is near the target tip pressure of 120 cm^2 (Table 5). The IMI further weights the value of suppuration for severe cases of disease as an integral part of the index, and thus limits potential false negatives in advanced cases where bleeding is no longer present [50]. This scoring system has been validated by a preclinical [40] and a clinical study [50], showing high reliability in monitoring peri-implant conditions. Moreover, the clinical study showed that single light bleeding points are not related to bone loss, thus negating the use of dichotomous BOP scales [50].

Suppuration

Pus is a turbid viscous inflammatory exudate consisting of dead leukocytes, microorganisms, necrotic tissues, and protein-rich fluid containing proinflammatory mediators and bacterial toxins [18, 29]. On the other hand, peri-implantitis lesions are more than twice as large as periodontitis sites (3.5 mm^2 versus 1.5 mm^2) [51]. In addition, peri-implantitis lesions are featured by larger area proportions, numbers, and densities of plasma cells, macrophages, neutrophils, and a higher density of vascular structures outside and lateral to the cell infiltrate compared with periodontitis sites [51]. These human data confirm findings from previous investigations [52, 53]. When compared with peri-implant mucositis, Gualini and Berglundh showed that peri-implantitis lesions were considerably larger and contained significantly greater proportions of B cells (CD19+) and elastase-positive cells than mucositis lesions [54]. Human studies have found that suppuration (SUP) is a likely event in peri-implantitis, but a

Table 3 Modified sulcular bleeding index (mSBI) [2]

Score	Description
0	No bleeding
1	Isolated spot bleeding
2	Blood forms a confluent red line or margin
3	Heavy or profuse bleeding

Table 4 Peri-implant mucosal tissue index [48]

Score	Condition	Description
0	Normal mucosa	Nothing remarkable
1	Mild inflammation	Slight color change, slight edema
2	Moderate inflammation	Redness, edema, and glazing
3	Severe inflammation	Marked redness, edema, ulceration as exemplified by spontaneous bleeding

Table 5 Implant mucosal index (IMI) [50]

Score	Description
0	No bleeding
1	Minimal, single-point bleeding
2	Moderate, multiple-point bleeding
3	Profuse, multiple-point bleeding
4	Suppuration

rare finding in the absence of disease [18, 44, 55]. In fact, observations from a recent canine study have shown that in more advanced presentations of ligature-induced peri-implantitis lesions, the odds for SUP are significantly higher [40]. Nevertheless, the absence of SUP does not necessarily indicate the absence of disease, since the acute phase of the inflammatory process is followed by new connective tissue formation that could mask the condition [56]. This therefore underscores the need to combine graded bleeding on probing to evaluate acute lesions and SUP in advanced or chronic lesions (Fig. 3).

Secondary Diagnostic Tools

The use of biomarkers was introduced with the aim of compensating the inconsistencies related to the clinical parameters used for the diagnosis/monitoring of periodontal and peri-implant conditions. Briefly, a biomarker is a measurable indicator of a biological/pathological process with the potential of anticipating clinically evident scenarios. In peri-implantitis for instance, inflammatory osteoclastogenesis represents the central pathological feature, which is mediated by proinflammatory mediators and regulators of osteoclastogenesis such as the receptor activator nuclear factor kappa-B (RANK), its ligand (RANKL) and osteoprotegerin (OPG). The latter inhibits RANKL interaction [57]. Hence, the interaction between RANK-RANKL leads to the differentiation of osteoclast progenitors and to the activity of mature osteoclasts. Osteoprotegerin on the other hand antagonizes this differentiation. Hence, it might be speculated that the expression of these factors may assist in monitoring peri-implant conditions.

Other markers have been identified with the dynamic process of bone remodeling, such as cathepsin-K, which degrades bone matrix, or sclerostin, which negatively regulates bone formation by reducing the mineral content of the bone.

Recent findings have contributed to elucidate the potential of RANK, RANKL, and OPG levels for assisting the diagnosis of peri-implantitis [59–62]. Likewise, cathepsin-K levels have been shown to be increased in peri-implantitis samples when compared with healthy peri-implant conditions, and to be positively correlated to PPD, BOP, and plaque index [63]. Interestingly, Rakic et al. demonstrated that this marker could potentially lead to the accurate diagnosis of mucositis, but not of peri-implantitis. Therefore, cathepsin-K could be expressed in the early osteoclastogenic process and at peri-implantitis onset [59]. More recently, the same research group evidenced the increased accuracy in diagnosing peri-implantitis when combining clinical parameters such as PPD, BOP > 0.25% with RANKL ≤ 19.9 pg/site. The same clinical features and RANKL > 19.9 pg/site in turn were indicative of mucositis [58] (Fig 4).

Other biomarkers of periodontal tissue inflammation, matrix degradation/regulation, and alveolar bone turnover/resorption have been linked with osteoclastic activity in response to inflammation around teeth and implants. For

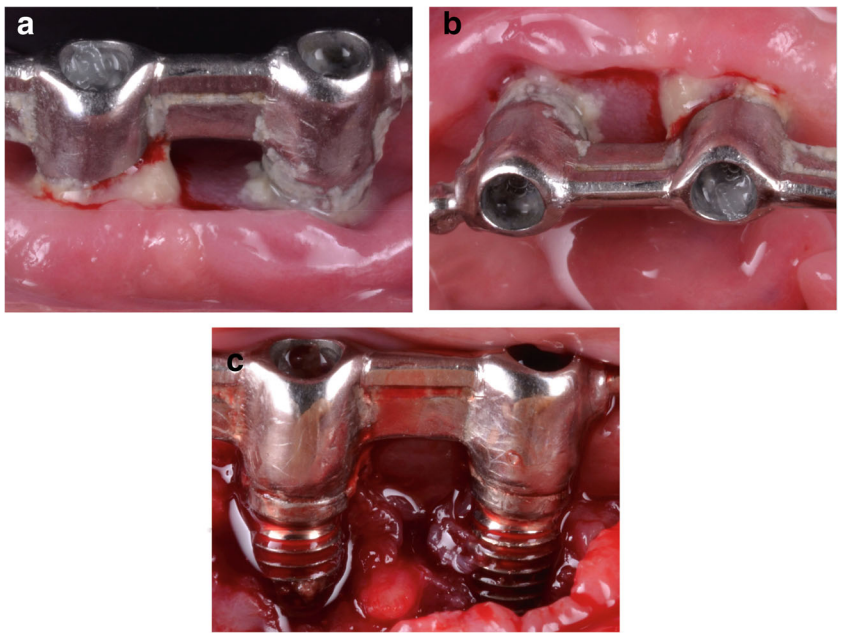

Fig. 3 Spontaneous suppuration is very often associated to advances forms of peri-implantitis with a hopeless or unfavorable prognosis

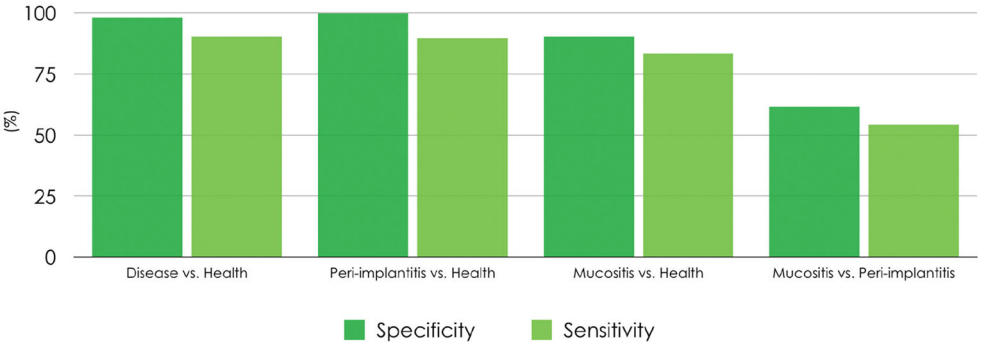

Fig. 4 Accuracy in diagnosing peri-implant diseases exclusively based on clinical parameters [58]

instance, there is a consistent evidence on the potential role of cytokines such as IL-B, TNF-a or IL-6, and MMP-8 in distinguishing peri-implantitis sites from healthy sites [64–66]. Nevertheless, their accuracy in identifying peri-implantitis versus mucositis remains controversial.

It must be underscored that conflicting evidence has been published concerning the use of biomarkers for the diagnosis of peri-implantitis. Moreover, the inflammatory expression of the early stages of the disorder is significantly stronger than in periodontal disease [67••]. Hence, these biomarkers should be used as a complement to the primary diagnostic tools.

Conclusions

The following conclusions can be drawn from the present review:

- The routine clinical assessment of dental implants, including probing and visual examination, may lead to the accurate diagnosis of peri-implant disorders. Nevertheless, the definitive diagnosis should be based on agreement with progressive radiographic bone loss.
- Primary diagnostic tools seem to be highly specific for monitoring peri-implant conditions, while their sensitivity is lower compared with their use in monitoring periodontal stability.
- Clinical parameters gain in accuracy when reported on a longitudinal basis and when clinical and radiographic changes are evaluated.
- Probing pocket depth is generally a reliable indicator of peri-implant disease if associated to bleeding, erythema, and/or suppuration.
- Single spots of light bleeding on probing may not reflect peri-implant disease, since implants are prone to exhibit bleeding on probing related to probe force. Hence, the use of dichotomous scales on bleeding on probing might lead to false positive diagnoses.
- Suppuration, until recently not part of any peri-implant index, is valuable, since it can assist the clinician in grading the severity of peri-implant disease, especially in advanced cases. Nonetheless, the accuracy of this parameter remains to be confirmed.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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