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Bleeding on probing around dental implants: a retrospective study of associated factors

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"Bleeding on probing around dental implants: a retrospective study of associated factors"

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AUTHORS' RESPONSE TO THE ISSUES RAISED BY THE REFEREES

Referee: 1

In general, the paper is well written and easy to read. The finding that the presence of BoP is associated with PD around implants is potentially important. The authors imply that BoP has "diagnostic and prognostic value". However, the Introduction only briefly mentions the presumed clinical importance of BoP, and the Discussion section of the paper does not adequately develop this theme. For example, are BoP+ sites at an increased risk of developing peri-implantitis (around implants) or periodontitis (around teeth)? How does the clinical importance of BoP compare with other signs of inflammation around implants (e.g., redness, swelling, purulent exudate)? Why should clinicians care if there is BoP around an implant?

IN ACCORDANCE WITH THE INDICATIONS OF THIS REFEREE, WE HAVE IMPLEMENTED THE INTRODUCTION SECTION WITH ADDITIONAL INFORMATION ON BOP. IN PARTICULAR, WE HAVE STRESSED THE CLINICAL ROLE OF BOP IN THE DIAGNOSIS OF PERIODONTAL AND PERI-IMPLANT DISEASES AS WELL AS ITS RELEVANCE WHEN USED TO IDENTIFY PATIENTS/SITES AT RISK FOR PERIODONTAL OR PERI-IMPLANT DETERIORATION: "In clinical periodontology, the diagnostic relevance of bleeding upon gentle (< 0.25 N) mechanical stimulation of the sulcus/pocket (bleeding on probing, BoP) is well recognized (Mühlemann & Son 1971, Lenox & Kopczyk 1973, Greenstein et al. 1981, Weinberg & Hassan 2012). BoP has also been shown to have a high negative predictive value for future disease progression. In particular, a high probability of of stable periodontal conditions was observed over time for BoP-negative sites (Lang et al. 1990, Newbrun 1996). Moreover, patients under maintenance care showing a full-mouth BoP score ≤ 20% were found at a lower risk for progressive attachment loss (Joss et al. 1994). Therefore, BoP is one of the parameters included in different methods for periodontal risk assessment (Page et al. 2002, Lang & Tonetti 2003, Renvert & Persson 2004, Trombelli et al. 2009).

When assessed around dental implants, BoP is a key parameter to diagnose inflammation in the peri-implant mucosa. The assessment of BoP is currently identified as the clinical measure to distinguish between peri-implant health and disease (Jepsen et al. 2015), being an invariable diagnostic element of peri-implant mucositis and peri-implantitis (Lang et al. 1994, Heitz-Mayfield 2008, Zitzmann & Berglundh 2008, Lang & Berglundh 2011). The available evidence seems to indicate that peri-implant BoP has a prognostic value, its presence (or absence) being associated with the deterioration (or stability) of peri-implant conditions overtime. In a cohort of patients under a rigid maintenance program, a high proportion of implants with BoP at ≥50% of SPT visits showed a deterioration of peri-implant tissues above pre-determined clinical and radiographic thresholds (Luterbacher et al. 2000). Patients with peri-implant mucositis (diagnosed as the presence of BoP) showed a varying risk for conversion to peri-implantitis depending on adherence to maintenance protocol. After 5 years of supportive therapy, peri-implantitis was diagnosed in 18% of the complying patients and 43.9% of non-complying patients (Costa et al. 2012). At implant sites affected by peri-implantitis, the absence of BoP showed a high negative predictive value for progressing peri-implant breakdown, thus serving as an indicator for stable peri-implant conditions (Jepsen et al. 1996). Based on the above mentioned evidence, the reduction/elimination of BoP is considered as a treatment goal in the clinical management of peri-implant diseases (Graziani et al. 2012, Jepsen et al. 2015, Schwarz et al. 2015)."

1. Page 3 (Abstract, line 2 under Methods) – "To analyze the influence of patient-, implant-, and…" Use of the word "influence" implies causation. It is suggested that the text be changed to, "To analyze the association of patient-, implant-, and…"

DONE.

2. Page 4 (Practical implications) – Although statistically significant, the association between gender and BoP+ is not particularly impressive or convincing. Therefore it is suggested that the authors delete the following phrase, "…and screening campaigns for peri-implant health should focus particularly on women."

TO ADDRESS THIS ISSUE, WE HAVE REPHRASED THE PRINCIPAL FINDINGS AND THE PRACTICAL IMPLICATIONS OF THE CLINICAL RELEVANCE SECTION: "Principal findings: The probability of a peri-implant site to bleed upon probing was (i) associated with PD, implant position and gender, and (ii) similar to that of contralateral dental sites when controlling for PD. Practical implications: BoP is highly frequent around dental implants. Women, implants at anterior sextants and peri-implant sites with deep pockets seem particularly prone to manifest peri-implant BoP.".

3. Page 7 (Study population) – The study population is very heterogeneous and appears to be a convenience sample. The sample size is quite small considering the major differences among study participants with regards to age, number of teeth and implants present, smoking history, and uncertainties regarding the length of time that the implants had been in place.

AS HYPOTHESIZED BY THE REFEREE, THE STUDY POPULATION CONSISTS OF A CONVENIENCE SAMPLE OF PATIENTS IDENTIFIED AMONG THOSE SEEKING CARE AT THE RESEARCH CENTRE FOR THE STUDY OF PERIODONTAL AND PERI-IMPLANT DISEASES, UNIVERSITY OF FERRARA, AND REHABILITATED WITH AT LEAST ONE DENTAL IMPLANT. THIS ASPECT HAS BEEN MADE CLEAR IN THE MATERIALS AND METHODS: "A convenience sample of adult (≥ 18 years old) patients presenting at least one osseointegrated (i.e., non-mobile) dental implant loaded for at least 3 months was collected for analysis.". THE DATABASE OF THE RESEARCH CENTRE COUNTS MORE THAN 1000 PATIENT RECORD CHARTS, 112 OF WHICH WERE AVAILABLE FOR THE PRESENT ANALYSIS. THE AUTHORS AGREE WITH THE REFEREE THAT THE PATIENT SAMPLE IS CHARACTERIZED BY A HIGH HETEROGENEITY RELATED TO SEVERAL PARAMETERS INCLUDING AGE, NUMBER OF TEETH AND IMPLANTS PRESENT, SMOKING HISTORY, AND TIME FROM IMPLANT PLACEMENT. GIVEN THE PURPOSE OF OUR STUDY, HOWEVER, THIS HETEROGENEITY WAS NECESSARY TO ALLOW FOR OUR MULTIVARIATE ANALYSIS TO IDENTIFY THOSE FACTORS SIGNIFICANTLY ASSOCIATED WITH PERI-IMPLANT BOP.

Were the study participants on a structured program of maintenance or supportive care? If so, how compliant were they with the recommended maintenance interval? Were there any data on oral hygiene skills of the participants? These factors may be important in the % of BoP+ sites. Perhaps at least as important as probing depths?

PATIENTS INCLUDED IN THE PRESENT ANALYSIS SHOWED A HIGH HETEROGENEITY IN TERMS OF TYPE AND FREQUENCY OF SUPPORTIVE PERIODONTAL THERAPY AS WELL AS IN TERMS OF ADHERENCE TO THE SUGGESTED PROGRAM (EITHER PERFORMED AT THE GENERAL PRACTITIONER OR AT OUR UNIVERSITY CENTER). THESE INFORMATION, HOWEVER, COULD NOT BE RETRIEVED FOR THE GREAT MAJORITY OF OUR POPULATION DUE TO THE FACT THAT ONLY PART OF THE ANALYZED PATIENT SAMPLE UNDERWENT SPT AT OUR CENTER. HOWEVER, WE DECIDED TO INCLUDE THE TIME ELAPSED FROM THE LAST SESSION OF SPT (WHICH COULD BE RETRIEVED FOR 100% POF PATIENTS) AS A COVARIATE, WHICH APPEARS RELEVANT FOR ITS POTENTIAL ASSOCIATION WITH BOP IN A SINGLE VISIT. THE ASSUMPTION WAS THAT BOP SHOULD BE EVALUATED IN RELATION TO 1) THE TIME FROM THE LAST INSTRUMENTATION OF THE IMPLANT SURFACE, AND 2) THE LOCAL CONDITIONS FAVORING THE RE-ESTABLISHMENT OF THE ORAL BIOFILM ON IMPLANT SURFACE (I.E., PROBING DEPTH).

WITH REGARD TO THE LEVEL OF ORAL HYGIENE OF STUDY PARTICIPANTS, WE AGREE WITH THE REVIEWER THAT OUR SITE-SPECIFIC ANALYSIS ON BOP SHOULD HAVE CONSIDERED SITE-SPECIFIC PLAQUE SCORE FOR ITS POTENTIAL ASSOCIATION WITH BOP. THIS PARAMETER, HOWEVER, COULD NOT BE RETRIEVED FOR A SUFFICIENT NUMBER OF PATIENTS TO ALLOW FOR A

STATISTICAL EVALUATION. THIS LIMITATION OF THE STUDY IS NOW REPORTED IN THE DISCUSSION SECTION: "Data on site-specific plaque levels around dental implants and contralateral teeth could not be retrieved for a number of record charts sufficient to allow for statistical evaluation. The positive relationship between supragingival plaque deposits and severity of supracrestal soft tissue inflammation is well demonstrated around either teeth (Loe et al. 1965, Trombelli et al. 2004, Muller 2009) or dental implants (Pontoriero et al. 1994, Salvi et al. 2012). However, the variability in BoP either among or within individuals can not be merely explained by quantitative nor qualitative differences in plaque accumulation (Abbas et al. 1986, Muller et al. 2000, Trombelli et al. 2004, 2008). In particular, the risk for gingival bleeding in presence of supragingival plaque varies markedly at the subject- and tooth-level (Muller et al. 2000). These findings represented the rationale for the present and previous studies investigating the impact of subject-related and site-specific factors on BoP variability around teeth (Farina et al. 2011, 2013).".

4. Page 7 (line 11 under Study population) – Should "marked emergency profile" be "marked emergent profile"? The authors should consider using the term "over-contoured implant-supported crowns."
WE PREFERRED TO OMIT THIS PART OF THE SENTENCE.

5. Page 7 (lines 14-15 under Study population) –"…no restoration extending below the gingival margin" Instead of the word "below" it is suggested it be replaced by "apical to". It is assumed that some upper teeth might have been included in the study sample and therefore the word "below" would not be appropriate.
THIS CRITERIUM HAS BEEN OMITTED (SEE RESPONSE TO THE NEXT COMMENT).

Why was this exclusion criteria chosen? Certainly many of the implants had margins of the superstructure crown that were apical to the mucosal margin.
WE THANK THE REFEREE FOR THIS COMMENT. WE HAVE RE-CHECKED THE MATERIAL FOR THE SELECTION CRITERIUM AND, SINCE TEETH WERE INCLUDED INDEPENDENTLY OF THE POSITION OF THE RESTORATION MARGIN (IF PRESENT) WITH RESPECT TO THE GINGIVAL MARGIN, WE DECIDED TO OMIT THIS CRITERIUM.

6. Page 8 (line 8) – "…examiners with long-term expertise in periodontal research…" How many calibrated examiners collected the data? Because the clinical data appear to have been collected on a convenience sample of "clinical record charts", were the data gathered under similar or different clinical circumstances? Were the data collected as part of a rigorous study protocol or were they extracted from charts filled out as part of day-to-day routine clinical practice? The levels of care and scrutiny in collection and recording of data differ between research and routine situations. Please clarify.
THE NUMBER OF EXAMINERS IS NOW EXPLICITLY REPORTED IN THE MATERIALS AND METHODS: "Probing recordings, including BoP, had been performed by five periodontists with long-term expertise in periodontal research. More specifically, all examiners had been previously involved in clinical trials including calibration sessions for the assessment of the main clinical probing parameters.". CLINICAL ASSESSMENTS HAD BEEN PERFORMED DURING CONVENTIONAL, ROUTINE VISITS USING A STANDARDIZED PATIENT RECORD CHART. IN ORDER TO DETERMINE PATIENT ELIGIBILITY FOR THE STUDY, THE TWO OPERATORS OF THIS STUDY DID NOT NEED A STANDARD OPERATING PROCEDURE, BUT RATHER HAD TO VERIFY ONLY 1) THE PRESENCE OF AT LEAST ONE OSSEOINTEGRATED DENTAL IMPLANT LOADED FOR AT LEAST 3 MONTHS, AND 2) THE AVAILABILITY OF A FULL-MOUTH PROBING ASSESSMENT PERFORMED AT LEAST 3 MONTHS FOLLOWING IMPLANT LOADING. FOR DATA EXTRACTION, THE PRINCIPAL AND SENIOR INVESTIGATOR OF THE STUDY HAD PREPARED A MICROSOFT EXCEL DATABASE, AND THE TWO OPERATORS TRANSFERRED ALL DATA OF INTEREST DIRECTLY INTO THE DATABASE: "Data from clinical record charts were obtained by 2 independent operators (M.F. and J.B.), entered into a Microsoft Excel™ file, and transferred into a statistical software

specifically designed for multilevel analysis (MLWin 2.32, Centre for Multilevel Modelling, Bristol University, UK). The site was considered as the statistical unit for analysis.".

7. Page 11 (line 13) – "A significant, positive correlation of 0.11 was observed…" Were correlation coefficients (r) values calculated? This is not clear from the Materials & Methods section or the Tables. A correlation coefficient of r = 0.11 is not impressive. In such circumstances a p value of 0.03 has no meaning.
THE CORRELATION COEFFICIENT (r) IS CALCULATED FROM THE COVARIANCE MATRIX OF THE MODEL. WE AGREE THAT THE CORRELATION BETWEEN THE 2 OUTCOME VARIABLES IS LIMITED, BUT WE STILL THINK THIS IS A RELEVANT INFORMATION FOR THE READER, AS THE OBJECTIVE OF THE STUDY WAS TO INVESTIGATE BOP AROUND IMPLANT AND TEETH. THE P VALUE IS REPORTED FOR INFORMATIVE PURPOSES AND NO SPECIFIC CONCLUSION HAS BEEN STATED FROM THAT.

8. Page 11 (First sentence of the Discussion section) – Please recast the entire sentence. As written, it makes no sense. The phrase starting with "…and patient as well as site…" is particularly awkward.
AS REQUESTED, WE HAVE REPHRASED THE FIRST SENTENCE OF THE DISCUSSION AS FOLLOWS: "The present study was performed to evaluate the association between BoP (as assessed at the site level around dental implants) and patient and site characteristics in a large cohort seeking care at a specialist periodontal centre.".

9. Page 12 (line 22) – Change "Consistently with…" to "Consistent with…"
DONE.

10. Page 13 (lines 8-14) – The material beginning with "Overall, these data…" is overly speculative and questionable considering that the convenience sample was small and heterogeneous.
CONSIDERING THE RESULTS OF THE STATISTICAL ANALYSIS, WE HAVE REPHRASED THE SENTENCE AS FOLLOWING: "Overall, these data seem to indicate that females are more prone to manifest bleeding of the peri-implant tissues upon probe stimulation.".

11. Page 13 (lines 20-23) – Recast the entire awkward sentence that begins with, "At dental implants and contralateral teeth…"
THE SENTENCE WAS REPHRASED AS FOLLOWS: "When BoP was considered irrespective of PD, the prevalence of units with no BoP+ sites was 41.2% and 39.4% at dental implants and contralateral teeth, respectively. The prevalence increased to 75.9% and 77.6% when BoP was associated with a deep pocket (Table 2).".

12. Page 13 (line 25) – "…may have been characterized by similar extension around the unit…" This is unclear. Please recast.
THE ENTIRE PARAGRAPH HAS BEEN CHANGED AND NOW READS AS FOLLOWS: "Together with findings from our previous study on BoP around teeth (Farina et al. 2013), the present results demonstrated that PD has a strong, positive relationship with BoP probability also around implants. Comparison between teeth and implants showed that, when controlling for PD and other factors influencing BoP (i.e. gender, tooth/implant position), a similar probability for a site to bleed upon probing was found at implant and tooth sites. Moreover, at implant- and tooth-level, a similar distribution pattern according to the number of BoP+ sites was also observed, particularly when BoP+ pockets were analyzed (Table 3). Our results corroborate and expand the findings of previous studies comparing the prevalence of BoP around implants and contralateral teeth. In the study by Vered et al. (2011), mean BoP was 0.77 for implants and 0.85 for contralateral teeth,

with no significant differences even when genders were considered separately (Vered et al. 2011). No statistically significant differences in the sulcus bleeding index (and PD) around dental implants and adjacent natural teeth were observed by Pontoriero et al. (1994) under either real life conditions or following acute, experimentally-induced plaque accumulation. In the study by Bragger et al. (1997), BoP was found at 24% of implant sites and 12% of tooth sites, but this difference was associated with a higher PD at dental implants compared to teeth. Despite the observed differences in probe penetration within the peri-implant/periodontal tissues in different healthy or diseased conditions (Schou et al. 2002, Abrahamsson & Soldini 2006), our findings suggest that BoP manifests similarly around dental implants and contralateral teeth, and the effect of PD seems to account for BoP variability more than the anatomical or patho-physiological characteristics inherent in peri-implant rather than periodontal tissues. For this reason, PD reduction should be regarded as a treatment endpoint to control BoP in prevention and therapeutic strategies of periodontal and peri-implant diseases.".

13. Page 14 (line 10) – What is "loss of the lingual compacta"? Do the authors mean that the lingual plate of compact bone has been lost? Please clarify.
"LINGUAL COMPACTA" IS NOW REPLACED BY "LINGUAL BONY WALL".

14. Pages 11-15 (Discussion section) – It is recommended that the Discussion section spend some time on helping readers understand the potential clinical importance of BoP on implant survival and peri-implantitis.
WE HAVE INCORPORATED ADDITIONAL INFORMATION ON THE RELATIONSHIP BETWEEN BOP AND PERI-IMPLANTITIS IN THE INTRODUCTION SECTION. FURTHERMORE, BASED ON THE SUGGESTION OF THE REFEREE WE HAVE PERFORMED A LITERATURE SEARCH TO IDENTIFY STUDIES SHOWING A DIRECT ASSOCIATION BETWEEN BOP AND IMPLANT SURVIVAL, BUT FAILED TO FIND PERTINENT ARTICLES.

Referee: 2
Introduction:
The introduction, especially the first paragraph, is not critical enough. It could be made more attractive by beginning with the controversy about utility and diagnostic value of BOP at implants and teeth. Critics warn that the BOP overrates the prevalence of disease due to high risk for false positive readings, as demonstrated in healthy subjects and successfully treated patients. This reviewer is unaware of hard prospective evidence of an increased risk for peri-implantitis at BOP positive implants. Specific, recent references should be used instead of citing general and in part outdated review papers. Such an introduction would provide a much stronger reason to conduct the presented analysis.
AS SUGGESTED BY THE REFEREE, WE HAVE IMPLEMENTED THE INTRODUCTION SECTION WITH ADDITIONAL INFORMATION ON BOP. IN PARTICULAR, WE HAVE STRESSED THE CLINICAL ROLE OF BOP IN THE DIAGNOSIS OF PERIODONTAL AND PERI-IMPLANT DISEASES AS WELL AS ITS RELEVANCE WHEN USED TO IDENTIFY SITES/PATIENTS AT RISK FOR PERIODONTAL OR PERI-IMPLANT DETERIORATION. SINCE THE PROGNOSTIC VALUE OF BOP WHEN ASSESSED AROUND DENTAL IMPLANTS REMAINS BASED ON A LIMITED NUMBER OF DATED STUDIES, WE HAVE MITIGATED THE PROGNOSTIC RELEVANCE OF BOP. THE INTRODUCTION (FIRS TWO PARAGRAPHS) NOW READS AS FOLLOWS: "In clinical periodontology, the diagnostic relevance of bleeding upon gentle (< 0.25 N) mechanical stimulation of the sulcus/pocket (bleeding on probing, BoP) is well recognized (Mühlemann & Son 1971, Lenox & Kopczyk 1973, Greenstein et al. 1981, Weinberg & Hassan 2012). BoP has also been shown to have a high negative predictive value for future disease progression. In particular, a high probability of of stable periodontal conditions was observed over time for BoP-negative sites (Lang et al. 1990, Newbrun 1996). Moreover, patients under maintenance care showing a full-mouth BoP score ≤ 20% were found at a lower risk for progressive attachment loss (Joss et al. 1994). Therefore, BoP is one of the

parameters included in different methods for periodontal risk assessment (Page et al. 2002, Lang & Tonetti 2003, Renvert & Persson 2004, Trombelli et al. 2009).
When assessed around dental implants, BoP is a key parameter to diagnose inflammation in the peri-implant mucosa. The assessment of BoP is currently identified as the clinical measure to distinguish between peri-implant health and disease (Jepsen et al. 2015), being an invariable diagnostic element of peri-implant mucositis and peri-implantitis (Lang et al. 1994, Heitz-Mayfield 2008, Zitzmann & Berglundh 2008, Lang & Berglundh 2011). The available evidence seems to indicate that peri-implant BoP has a prognostic value, its presence (or absence) being associated with the deterioration (or stability) of peri-implant conditions overtime. In a cohort of patients under a rigid maintenance program, a high proportion of implants with BoP at ≥50% of SPT visits showed a deterioration of peri-implant tissues above pre-determined clinical and radiographic thresholds (Luterbacher et al. 2000). Patients with peri-implant mucositis (diagnosed as the presence of BoP) showed a varying risk for conversion to peri-implantitis depending on adherence to maintenance protocol. After 5 years of supportive therapy, peri-implantitis was diagnosed in 18% of the complying patients and 43.9% of non-complying patients (Costa et al. 2012). At implant sites affected by peri-implantitis, the absence of BoP showed a high negative predictive value for progressing peri-implant breakdown, thus serving as an indicator for stable peri-implant conditions (Jepsen et al. 1996). Based on the above mentioned evidence, the reduction/elimination of BoP is considered as a treatment goal in the clinical management of peri-implant diseases (Graziani et al. 2012, Jepsen et al. 2015, Schwarz et al. 2015)."

Material and methods:
"Data from clinical record charts were obtained by two independent operators". Many essential details are missing:
Subjects:
1. How were the subjects selected? Was this a random sample (it seems not to be the case)?
THIS ASPECT IS NOW MADE CLEAR IN THE MATERIALS AND METHODS: "De-identified data were retrospectively derived from the clinical record charts of patients seeking care at the Research Centre for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy. …A convenience sample of adult (≥ 18 years old) patients presenting at least one osseointegrated (i.e., non-mobile) dental implant loaded for at least 3 months was collected for analysis.".

2. Were all implants assessed in each subject? If not, what were the inclusion and exclusion criteria?
THE FOLLOWING SENTENCE WAS ADDED TO THE MATERIALS AND METHODS SECTION IN ORDER TO CLARIFY THIS ASPECT: "For each patient, all implants were considered for analysis.".

3. Is it one cohort or were there several groups? One city or several places of assessment? Were participants recruited from patients of a clinic, private practice, …?
IN THE MATERIALS AND METHODS, WE HAVE STATED THAT "De-identified data were retrospectively derived from the clinical record charts of patients seeking care at the Research Centre for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy.". THEREFORE, THE PRESENT ANALYSIS WAS PERFORMED ON A SINGLE COHORT OF SUBJECTS ATTENDING A SPECIALIST UNIVERSITY CENTER, WHERE ALL ASSESSMENTS WERE PERFORMED.

4. Reasons for tooth loss (periodontal disease)? Were they in regular maintenance? Etc.
DUE TO THE RETROSPECTIVE NATURE OD THE STUDY, IT IS NOT POSSIBLE TO RETRIEVE INFORMATION ON THE REASON FOR TOOTH LOSS. MOREOVER, SOME PATIENTS INCLUDED IN THE PRESENT COHORT HAD ALREADY UNDERGONE TOOTH REPLACEMENT WITH AN IMPLANT-SUPPORTED RESTORATION BEFORE PRESENTING AT OUR CENTER FOR FIRST VISIT, AND COULD NOT RECALL THE REASON FOR TOOTH LOSS/EXTRACTION. ALTHOUGH THIS INFORMATION MAY

WOULD HAVE HELPED TO BETTER DEFINE THE PERIODONTAL STATUS OF THE PATIENTS, REASONS TOOTH LOSS WAS REGARDED OF LIMITED INTEREST IN VIEW OF THE STUDY AIM.
IN THE PRESENT MATERIAL, PATIENTS WERE INCLUDED FOR ANALYSIS IF A VISIT, PERFORMED AT LEAST 3 MONTHS FOLLOWING IMPLANT LOADING AND INCLUDING A FULL-MOUTH PROBING ASSESSMENT, WAS AVAILABLE FOR DATA EXTRACTION. THEREFORE, WHILE SOME PATIENTS HAD NEVER UNDERGONE ACTIVE PERIODONTAL THERAPY AT FIRST VISIT, OTHERS HAD BEEN ENROLLED IN A MAINTENANCE PROGRAM. PATIENTS UNDER MAINTENANCE CARE SHOWED A HIGH HETEROGENEITY IN TERMS OF TYPE AND FREQUENCY OF MAINTENANCE SESSIONS AS WELL AS IN TERMS OF ADHERENCE TO THE SUGGESTED PROGRAM. THESE INFORMATIONS, HOWEVER, COULD NOT BE RETRIEVED FOR THE GREAT MAJORITY OF OUR POPULATION DUE TO THE FACT THAT ONLY PART OF THE ANALYZED PATIENT SAMPLE UNDERWENT SPT AT OUR CENTER. HOWEVER, WE DECIDED TO INCLUDE THE TIME ELAPSED FROM THE LAST SESSION OF SPT (WHICH COULD BE RETRIEVED FOR 100% POF PATIENTS) AS A COVARIATE, WHICH APPEARS RELEVANT FOR ITS POTENTIAL ASSOCIATION WITH BOP IN A SINGLE VISIT.

Assessments:
5. Were the data assessed for the purpose of the study? If not, in what context were they obtained? The date/time-span of the evaluations and the data retrieval should be given.
CLINICAL PARAMETERS WERE ASSESSED DURING CONVENTIONAL CLINICAL ACTIVITY. DATA WERE EXTRACTED FROM SELECTED RECORD CHARTS FOR THE PURPOSE OF THIS SPECIFIC STUDY, WITH THE APPROVAL OF THE LOCAL ETHICAL COMMITTEE. THE DATES/PERIOD FOR CLINICAL ASSESSMENTS AND DATA EXTRACTION ARE NOW REPORTED IN THE MATERIALS AND METHODS: " De-identified data were retrospectively derived from the clinical record charts of patients seeking care at the Research Centre for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy, in the years 1999-2015. The study protocol was approved by the Local Ethical Committee (protocol number: 160182; date of approval: March 17, 2016). Data extraction was performed between April and July, 2016.".

6. Who assessed the parameters in the patients? Some of the authors, or somebody else? How many persons were involved?
THE REQUESTED INFORMATION ARE NOW REPORTED IN THE MATERIALS AND METHODS: "Probing recordings, including BoP, had been performed by five periodontists with long-term expertise in periodontal research. More specifically, all examiners had been previously involved in clinical trials including calibration sessions for the assessment of the main clinical probing parameters.". ONE OF THE AUTHORS (R.F.) WAS ONE OF THE CLINICAL EXAMINERS.

7. Were the assessors calibrated? Were they periodontists, GPs, dental hygienists, dental assistants, …?
AS NOW STATED IN THE MATERIALS AND METHODS, "… five periodontists with long-term expertise in periodontal research.…all examiners had been previously involved in clinical trials including calibration sessions for the assessment of the main clinical probing parameters.". DUE TO THE RETROSPECTIVE NATURE OF THE EXPERIMENTAL DESIGN, HOWEVER, NO CALIBRATION SESSION COULD BE PERFORMED *AD HOC* FOR THIS STUDY, THUS PREVENTING THE POSSIBILITY TO EVALUATE THE LEVEL OF INTER- AND INTRA- EXAMINER AGREEMENT IN THE ASSESSMENT OF CLINICAL PARAMETERS, IN GENERAL, AND BOP, IN PARTICULAR.

8. Were the assessments made using a standard operating procedure?
CLINICAL ASSESSMENTS HAD BEEN PERFORMED DURING CONVENTIONAL VISITS USING STANDARDIZED PATIENT RECORD CHART. FOR DATA EXTRACTION, DATA WERE TRANSFERRED

FROM THE PATIENT RECORD CHARTS TO A MICROSOFT EXCEL™ FILE, AND SUBSEQUENTLY TO A STATISTICAL SOFTWARE SPECIFICALLY DESIGNED FOR MULTILEVEL ANALYSIS. THESE ASPECTS ARE ALL CLEAR IN THE MATERIALS AND METHODS: “Data from clinical record charts were obtained by 2 independent operators (M.F. and J.B.), entered into a Microsoft Excel™ file, and transferred into a statistical software specifically designed for multilevel analysis (MLWin 2.32, Centre for Multilevel Modelling, Bristol University, UK). The site was considered as the statistical unit for analysis.”.

Retrieval:

9. As the data were "retrieved" by two operators, what was the role of each? What means "independent"? Did they both read all data in duplicate?

THESE ASPECTS HAVE BEEN MADE CLEAR IN THE MATERIALS AND METHODS: “Data from clinical record charts were obtained by 2 independent operators (M.F. and J.B.), entered into two distinct Microsoft Excel™ (Microsoft Corporation, Peschiera di Borromeo, Milan, Italy) files. The two database files were compared, and discrepancies were solved between the operators by consulting the original patient record charts. A unique file was obtained, and all data were transferred into a statistical software specifically designed for multi-level analysis (MLWin 2.32; Centre for Multilevel Modelling, Bristol University, UK), and used for statistical analysis. The site was considered as the statistical unit for analysis.”.

10. Was there a standard operating procedure for data retrieval?

IN ORDER TO DETERMINE PATIENT ELIGIBILITY FOR THE STUDY, THE TWO OPERATORS DID NOT NEED A STANDARD OPERATING PROCEDURE, BUT RATHER HAD TO VERIFY ONLY 1) THE PRESENCE OF AT LEAST ONE OSSEOINTEGRATED DENTAL IMPLANT LOADED FOR AT LEAST 3 MONTHS, AND 2) THE AVAILABILITY OF A FULL-MOUTH PROBING ASSESSMENT PERFORMED AT LEAST 3 MONTHS FOLLOWING IMPLANT LOADING.

FOR DATA EXTRACTION, THE PRINCIPAL AND SENIOR INVESTIGATOR OF THE STUDY HAD PREPARED A MICROSOFT EXCEL DATABASE, AND THE TWO OPERATORS TRANSFERRED ALL DATA OF INTEREST DIRECTLY INTO THE DATABASE.

Ethical:

1. Were the patients informed about the study? Did they consent?

AN INFORMED CONSENT FORM HAD BEEN PREPARED SPECIFICALLY FOR THE STUDY. HOWEVER, THE ETHICAL COMMITTEE HAD BEEN INFORMED THAT THE COLLECTION OF SIGNED CONSENT FORMS WAS EXPECTED TO BE PARTICULARLY UNPRODUCTIVE DUE TO THE FOLLOWING REASONS: (I) SEVERAL PATIENTS WERE NOT ANYMORE SEEKING CARE AT THE UNIVERSITY OF FERRARA (MOST OF THEM HAD RETURNED TO THEIR GENERAL PRACTITIONER FOR PERIODONTAL MAINTENANCE); AND (II) THEIR CONTACTS (ADDRESS, TELEPHONE NUMBER, E-MAIL) REPORTED IN THE RECORD CHARTS HAD BEEN CHANGED THROUGH THE YEARS, THUS LIMITING THE POSSIBILITY TO CONTACT THEM AND OBTAIN THE CONSENT. AS EXPECTED, ONLY FEW INFORMED CONSENTS WERE RETRIEVED. HOWEVER, OUR ETHICAL COMMITTEE HAS GIVEN ITS FULL APPROVAL TO THE STUDY.

2. What was the role of each of five (!) authors? For an analysis of retrieved data this seems excessive. Honorary authorships are not acceptable.

DR. FARINA AND PROF. TROMBELLI WERE THE PRINCIPAL AND SENIOR INVESTIGATORS, RESPECTIVELY. THEY PREPARED THE STUDY PROTOCOL, OBTAINED ETHICAL APPROVAL, SUPERVISED DATA EXTRACTION AND PREPARED THE FINAL REPORT AS WELL AS THE PRESENT MANUSCRIPT. DR. FILIPPI AND DR. BRAZZIOLI PERFORMED THE SCREENING OF THE PATIENT RECORD CHARTS AND DATA EXTRACTION. DR. TOMASI PERFORMED THE STATISTICAL ANALYSIS

AND INCORPORATED THE DESCRIPTIVE AND INFERENTIAL STATISTICS IN THE RESULTS SECTION OF THE MANUSCRIPT.
THESE INFORMATION ARE NOW REPORTED IN THE FIRST PAGE OF THE MANUSCRIPT UNDER THE PARAGRAPH "AUTHORS' CONTRIBUTION TO THE STUDY".

Analysis:
The analysis should include a look at intra-examiner variation.
UNFORTUNATELY, THE RETROSPECTIVE NATURE OF THE EXPERIMENTAL DESIGN PREVENTED THE POSSIBILITY TO EVALUATE THE LEVEL OF INTER- AND INTRA- EXAMINER AGREEMENT IN THE ASSESSMENT OF CLINICAL PARAMETERS, IN GENERAL, AND BOP, IN PARTICULAR.

Referee: 3
1. Was the presence/absence of attached and keratinized tissue around implants and teeth considered in the model.
KERATINIZED TISSUE WIDTH WAS NOT CONSIDERED AS A COVARIATE IN THE PRESENT MULTIVARIATE ANALYSIS DUE TO THE INCONSISTENCY OF DATA RECORDING IN THE CLINICAL CHART. THE REASON FOR THE EXCLUSION OF THIS PARAMETER AS WELL AS SOME ADDITIONAL CONSIDERATION BASED ON THE EXISTING LITERATURE ARE NOW INCLUDED IN THE DISCUSSION: "The number of covariates was kept limited in order to preserve the power of our multivariate analysis. The reasons for the exclusion of some factors potentially associated with peri-implant BoP are different. …. Keratinized tissue width could not be retrieved in a high proportion of the patient record charts. To date, the relationship between keratinized mucosa and peri-implant BoP remains controversial. While recent studies suggest a possible association between BoP and amount of keratinized mucosa (Romanos et al. 2015, Ueno et al. 2016), previous systematic reviews failed to find a significant association (Lin et al. 2013) or did not retrieve sufficient data to perform an analysis (Gobbato et al. 2013)."

2. Was the presence/absence of excess cement around implant-supported restorations considered as a modifying factor affecting bleeding on probing.
THE AUTHORS FULLY AGREE WITH THE REVIEWER. SINCE DATA FROM RECENT STUDIES SUGGEST THAT EXCESS CEMENT IS ASSOCIATED WITH INCREASED PREVALENCE OF BOP (KORSCH ET AL. 2015), THE EXCESS CEMENT SHOULD HAVE BEEN INCLUDED AS A COVARIATE. UNFORTUNATELY, IMPLANTS WITH CEMENTED PROSTHESIS REPRESENTED ONLY A SUBPOPULATION OF OUR SAMPLE, AND NO DATA ON RESIDUAL CEMENT OBTAINED DURING A SURGICAL RE-ENTRY OR THROUGH RADIOGRAPHIC EXAMS WERE AVAILABLE FOR THE MAJORITY OF THESE IMPLANTS. THEREFORE, THIS PARAMETER COULD NOT BE INCLUDED IN OUR MULTIVARIATE ANALYSIS DUE TO THE LACK OF SPECIFIC INFORMATION.

3. Were different abutment or implant neck configurations considered as modifying factors affecting the access to record bleeding on probing.
AGAIN, THESE FACTORS COULD NOT BE INCORPORATED IN OUR ANALYSIS. THE REASON FOR EXCLUSION ARE REPORTED IN THE DISCUSSION SECTION: "The number of covariates was kept limited in order to preserve the power of our multivariate analysis. The reasons for the exclusion of some factors potentially associated with peri-implant BoP are different. The study population showed a highly dispersed distribution according to the configuration of the implant neck/abutment and the type of implant-supported restoration, thus preventing the possibility to compare subgroups of sufficient size.".

4. Were plaque scores around implants and teeth considered in the model.

WE AGREE WITH THE REVIEWER THAT OUR SITE-SPECIFIC ANALYSIS ON BOP SHOULD HAVE CONSIDERED SITE-SPECIFIC PLAQUE SCORE FOR ITS POTENTIAL ASSOCIATION WITH BOP. THIS PARAMETER, HOWEVER, COULD NOT BE RETRIEVED FOR A SUFFICIENT NUMBER OF PATIENTS TO ALLOW FOR A STATISTICAL EVALUATION. THIS LIMITATION OF THE STUDY IS NOW REPORTED IN THE DISCUSSION SECTION: “Data on site-specific plaque levels around dental implants and contralateral teeth could not be retrieved for a number of record charts sufficient to allow for statistical evaluation. The positive relationship between supragingival plaque deposits and severity of supracrestal soft tissue inflammation is well demonstrated around either teeth (Loe et al. 1965, Trombelli et al. 2004, Muller 2009) or dental implants (Pontoriero et al. 1994, Salvi et al. 2012). However, the variability in BoP either among or within individuals can not be merely explained by quantitative nor qualitative differences in plaque accumulation (Abbas et al. 1986, Muller et al. 2000, Trombelli et al. 2004, 2008). In particular, the risk for gingival bleeding in presence of supragingival plaque varies markedly at the subject- and tooth-level (Muller et al. 2000). These findings represented the rationale for the present and previous studies investigating the impact of subject-related and site-specific factors on BoP variability around teeth (Farina et al. 2011, 2013).”.

Bleeding on probing around dental implants: a retrospective study of associated factors

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Authors' contribution to the study
Dr. R. Farina and Prof. L. Trombelli were the Principal and Senior Investigator, respectively. They prepared the study protocol, obtained ethical approval, supervised data extraction and prepared the final report as well as the present manuscript. Dr. M. Filippi and Dr. J. Brazzioli performed the screening of the patient record charts and data extraction. Prof. C. Tomasi performed the statistical analysis and incorporated the descriptive and inferential statistics in the Results section of the manuscript.

Running title
The peri-implant bleeding site

Key words
Gingival hemorrhage; gingival pocket; periodontal pocket; inflammation; dental implants.

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ABSTRACT

Aim: to (i) identify factors associated with the probability of a peri-implant site to be positive to bleeding on probing (BoP+), and (ii) compare BoP+ probability around dental implants and contralateral teeth.

Methods: In 112 patients, data related to 1725 peri-implant sites and 1020 contralateral dental sites were retrospectively obtained. To analyze the association between patient-, implant- and site-related factors and BoP+ probability, a logistic, 3-level model was built with BoP as the binary outcome variable (+/-).

Results: BoP+ probability for a peri-implant site with probing depth (PD) of 4 mm was 27%, and the odds ratio increased by 1.6 for each 1-mm increment in PD ($p < 0.001$). Also, BoP+ probability was higher in females compared to males (OR= 1.61; $p = 0.048$), and lower at posterior compared to anterior dental implants (OR= 0.55; $p < 0.01$). No significant difference in BoP+ probability was observed between peri-implant and contralateral dental sites when controlling for the difference in PD.

Conclusions: The probability of a peri-implant site to bleed upon probing is (i) associated with PD, implant position and gender, and (ii) similar to that observed at contralateral dental sites when controlling for the effect of PD.

CLINICAL RELEVANCE

Scientific background: Around dental implants, bleeding on probing (BoP) has a diagnostic and prognostic value. Limited information is available on the modulatory effect of patient and site characteristics on the risk for peri-implant BoP.

Principal findings: The probability of a peri-implant site to bleed upon probing was (i) associated with PD, implant position and gender, and (ii) similar to that of contralateral dental sites when controlling for PD.

Practical implications: BoP is highly frequent around dental implants. Women, implants at anterior sextants and peri-implant sites with deep pockets seem particularly prone to manifest peri-implant BoP.

INTRODUCTION

In clinical periodontology, the diagnostic relevance of bleeding upon gentle (< 0.25 N) mechanical stimulation of the sulcus/pocket (bleeding on probing, BoP) is well recognized (Mühlemann & Son 1971, Lenox & Kopczyk 1973, Greenstein et al. 1981, Weinberg & Hassan 2012). BoP has also been shown to have a high negative predictive value for future disease progression. In particular, a high probability of of stable periodontal conditions was observed over time for BoP-negative sites (Lang et al. 1990, Newbrun 1996). Moreover, patients under maintenance care showing a full-mouth BoP score ≤ 20% were found at a lower risk for progressive attachment loss (Joss et al. 1994). Therefore, BoP is one of the parameters included in different methods for periodontal risk assessment (Page et al. 2002, Lang & Tonetti 2003, Renvert & Persson 2004, Trombelli et al. 2009).

When assessed around dental implants, BoP is a key parameter to diagnose inflammation in the peri-implant mucosa. The assessment of BoP is currently identified as the clinical measure to distinguish between peri-implant health and disease (Jepsen et al. 2015), being an invariable diagnostic element of peri-implant mucositis and peri-implantitis (Lang et al. 1994, Heitz-Mayfield 2008, Zitzmann & Berglundh 2008, Lang & Berglundh 2011). The available evidence seems to indicate that peri-implant BoP has a prognostic value, its presence (or absence) being associated with the deterioration (or stability) of peri-implant conditions overtime. In a cohort of patients under a rigid maintenance program, a high proportion of implants with BoP at ≥50% of SPT visits showed a deterioration of peri-implant tissues above pre-determined clinical and radiographic thresholds (Luterbacher et al. 2000). Patients with peri-implant mucositis (diagnosed as the presence of BoP) showed a varying risk for conversion to peri-implantitis depending on adherence to maintenance protocol. After 5 years of supportive therapy, peri-implantitis was diagnosed in 18% of the complying patients and 43.9% of non-complying patients (Costa et al. 2012). At implant sites affected by peri-implantitis, the absence of BoP showed a high negative predictive value for progressing peri-implant breakdown, thus serving as an indicator for stable peri-

implant conditions (Jepsen et al. 1996). Based on the above mentioned evidence, the reduction/elimination of BoP is considered as a treatment goal in the clinical management of peri-implant diseases (Graziani et al. 2012, Jepsen et al. 2015, Schwarz et al. 2015).

Factors influencing BoP around teeth have been widely investigated (Müller et al. 2000, Dietrich et al. 2004, Müller 2009, Müller & Barrieshi-Nusair 2010, Farina et al. 2011, 2013). In particular, we recently applied a multilevel statistical model to a dataset obtained from a large cohort of patients with different types of periodontal diseases in order to identify factors associated with the full-mouth prevalence of BoP (Farina et al. 2011) or the probability of a sulcus/pocket to be BoP positive (BoP+) (Farina et al. 2013). Our findings showed that the probability of a dental site to bleed upon probing is associated with either site-specific (i.e. probing depth, tooth type, tooth aspect) or patient-related factors (i.e. gender, smoking status) (Farina et al. 2013). To date, limited information is presently available on the modulatory effect of patient and site characteristics on the risk for BoP around dental implants. Moreover, even assuming that some of the factors influencing BoP around teeth may have an impact on peri-implant BoP, anatomical differences in the supracrestal peri-implant and periodontal soft tissue compartment (Berglundh et al. 1991, 1992, 1994, 1996) as well as differences in the extension and composition of the biofilm-related inflammatory infiltrate around dental implants and teeth (Ericsson et al. 1992, Liljenberg et al. 1997, Salvi et al. 2012) support the possibility that the peri-implant and dental sites may respond differently to the mechanical stimulation by periodontal probing.

Previous studies comparatively evaluated the prevalence of BoP around dental implants and contralateral control teeth, with contrasting results. While some studies reported a greater prevalence of BoP at dental implants compared to control teeth (Bragger et al. 1997), others failed to find significant differences (Vered et al. 2011). These studies mainly aimed at comparing the conditions of peri-implant and periodontal tissues rather than identifying BoP determinants. In fact, a mere descriptive analysis of

BoP prevalence was conducted, and factors potentially influencing BoP were not used as covariates to adjust a multi-level analysis. The aim of the present study was to evaluate the association between the probability of a peri-implant site to be BoP+, and patient as well as site characteristics in a large cohort of patients seeking care at a specialist periodontal clinic. Moreover, we comparatively evaluated the probability for a site to be BoP+ around either dental implants or contralateral teeth in a split-mouth model.

MATERIALS & METHODS

Experimental design and ethical aspects

De-identified data were retrospectively derived from the clinical record charts of patients seeking care at the Research Centre for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy, in the years 1999-2015. The study protocol was approved by the Local Ethical Committee (protocol number: 160182; date of approval: March 17, 2016). Data extraction was performed between April and July, 2016.

Study population

A convenience sample of adult (≥ 18 years old) patients presenting at least one osseointegrated (i.e., non-mobile) dental implant loaded for at least 3 months was collected for analysis. No specific inclusion criteria related to the patient medical/dental history, drug consumption, and peri-implant/periodontal status were adopted. For each patient, all implants were considered for analysis. The most recent visit, performed at least 3 months following implant loading and including a full-mouth probing assessment, was considered for data extraction.

Data from 112 patients (53 males and 59 females, mean age: 55.2 ± 12.1 years, range: 22 - 81) were retrieved for analysis (Figure 1). The characteristics of the study population are reported in Table 1.

Overall, 1734 sites at 289 dental implants (Table 2) had been evaluated for BoP assessment. For 9 sites it had not been possible to record BoP due to local conditions (e.g., presence of calculus, presence of a prosthetic superstructure) preventing proper probing recordings. For each dental implant, the availability of a contralateral tooth with the following characteristics was verified: same arch (maxilla, mandible) and position (incisor, canine, premolar, molar); no grade III mobility; no periapical lesions; vital or undergone proper endodontic treatment. Overall, data from 170 teeth in 103 patients with such characteristics were obtained and included for analysis.

BoP recordings

BoP had been recorded as positive (BoP+) when bleeding of the peri-implant mucosa (or gingiva) had been detected at implant (tooth) site level after probing depth (PD) assessment (Muhlemann & Son 1971, Mombelli et al.1987). PD had been measured as the distance from the mucosal (or gingival) margin to the bottom of the sulcus/pocket using a manual pressure sensitive probe (CP12; Hu-Friedy, Chicago, Illinois, US) with a force of about 0.2 N at 6 aspects for each dental implant/tooth (mesio-buccal, mid-buccal, disto-buccal, mesio-lingual, mid-lingual, disto-lingual). Probing recordings, including BoP, had been performed by five periodontists with long-term expertise in periodontal research. More specifically, all examiners had been previously involved in clinical trials including calibration sessions for the assessment of the main clinical probing parameters.

STATISTICAL ANALYSIS

Data from clinical record charts were obtained by 2 independent operators (M.F. and J.B.), entered into two distinct Microsoft Excel™ (Microsoft Corporation, Peschiera di Borromeo, Milan, Italy) files. The two database files were compared, and discrepancies were solved between the operators by consulting the original patient record charts. A unique file was obtained, and all data were transferred into a statistical software specifically designed for multi-level analysis (MLWin 2.32; Centre for Multilevel Modelling,

Bristol University, UK), and used for statistical analysis. The site was considered as the statistical unit for analysis.

To analyze the influence of patient-, implant- and site-related factors on the probability for a site to be BoP+, a logistic, 3-level model (patient, implant and site) was built with BoP+ as the binary outcome variable. The logit function was used to link the linear model with the probability of the binary event such that, if b is the intercept, the anti-logit function of the parameter b was calculated with the formula: $P(\text{BoP+}) = \exp(\beta) / [1 + \exp(\beta)]$ to obtain the probability for a site to be BoP+ (Snijders & Bosker 1999). The statistical methods used to estimate the covariates and test their significance replicated those of a previous study on factors associated with BoP around teeth (Farina et al. 2013).

The following parameters were investigated for their association with the probability of a site to be BoP+:

- site level: PD (mm); implant aspect [approximal (mid-buccal or mid-lingual) or interproximal (mesiobuccal, mesio-lingual, distobuccal, distolingual)].
- implant level: dental arch (maxillary or mandibular); position [posterior (molars/premolars) or anterior (canines/incisors)]; type of implant-supported prosthesis (crown, bridge, or removable); time from loading (months);
- patient level: age (20-29, 30-39, 40-49, 50-59, or ≥60 years); gender; time elapsed from the last full-mouth session of non-surgical periodontal treatment; smoking status (current smokers, non-smokers); daily cigarette consumption (1-9, 10-19, or ≥20 cigarettes/day); smoking exposure (packs * years of smoking); number of teeth present; number of dental implants; number of sites with PD≥ 5 mm around teeth.

The impact of each parameter on BoP variability was expressed as OR and 95% confidence interval (95%CI) for BoP+. The level of statistical significance was fixed at 5%. The final 3-level model included all factors that were found significant. The heteroskedasticity of the data (variance not constant) was verified by letting the variance randomly vary at patient level. The intra-class correlation (ICC), i.e. the proportion of the total variance attributed to the patient level, was calculated (Snijders & Bosker 1999).

A continuous model was built to evaluate the difference in BoP probability between implant and contralateral tooth sites. ΔBoP was calculated as the difference between peri-implant BoP (expressed as 1-positive or 0-negative) and BoP at contralateral tooth site (expressed as 1-positive or 0-negative), thus assuming the values -1, 0 or +1, and was used as the outcome variable. The model was controlled for the difference in PD between peri-implant and contralateral tooth site (ΔPD).

RESULTS

Identification of factors affecting the probability for a peri-implant site to be BoP+

Over 1725 peri-implant sites included for analysis, 478 (27.9%) sites from 246 dental implants in 85 patients were BoP+ while 1235 (72.1%) sites from 286 dental implants in 111 patients were BoP-. The distribution of dental implants according to the number of BoP+ sites (either irrespective of PD or associated with PD≥ 5 mm) per dental implant is reported in Table 3.

When applied without covariates, the multivariate model with peri-implant, site-specific BoP+ as outcome event (Table 4) revealed a probability of 22% (95%CI: 18% – 27%) for a site to be BoP+ in the average patient. The ICC showed that 22% of the variance in BoP+ probability at the site level was due to variation between patients, while the remaining 78% was due to variation between sites within each patient. When PD was entered into the model, a significant association between PD and BoP+

probability was found (p< 0.001). In particular, BoP+ probability for a peri-implant site with PD = 4 mm was 27% (95%CI: 22% – 32%) (Figure 2). For each 1 mm increment in PD, the odds ratio increased by 1.6 (95%CI: 1.43 – 1.77). Hence, the mean BoP+ probability for peri-implant sites with PD of 5 mm and 6 mm was 37% and 48%, respectively (Figure 2). The model including PD explained 10% of the BoP variability at the site-level (R^2 = 0.10) (Table 4). The other covariates were then introduced one by one and tested for their influence on the probability for a peri-implant site to be BoP+, controlling for PD. Females showed a higher BoP+ probability compared to males (OR= 1.61, 95%CI: 1.00 – 2.57; p= 0.048). Also, peri-implant sites had a lower probability to be BoP+ when located at posterior dental implants compared to anterior dental implants (OR= 0.55, 95%CI: 0.36 – 0.83; p< 0.01) (Table 4).

On the basis of the findings from the multivariate analysis, the probability for a peri-implant site to be BoP+ was stratified according to significant covariates (i.e., gender, PD and implant position) (Figure 3). The effect of gender and implant position was less evident at sulci (i.e. PD= 1–2 mm) and deep pockets (i.e. PD≥ 9 mm), thus suggesting that the effect of PD on BoP+ probability was more relevant than the effect of the other factors (Figure 3).

BoP+ probability at dental implants and contralateral tooth sites

In the 170 couples of dental implants and contralateral teeth, 241 (23.6%) peri-implant sites and 246 (24.1%) dental sites were BoP+. The distribution of teeth according to the number of BoP+ sites per tooth was not significantly different from that observed for implants (Table 3).

A significant, positive correlation of 0.11 was observed at patient-level between BoP+ probability at implant and tooth sites (p= 0.03). The multilevel model with ΔBoP as outcome variable showed that no significant difference in BoP probability was observed between teeth and implants when controlling for ΔPD (p= 0.30).

DISCUSSION

The present study was performed to evaluate the association between BoP (as assessed at the site level around dental implants) and patient and site characteristics in a large cohort seeking care at a specialist periodontal centre. Moreover, we comparatively evaluated the probability for a site to be BoP+ around either dental implants or contralateral teeth in a split-mouth model. Data related to 1725 sites from 289 implants and 1020 sites from 170 contralateral teeth were retrospectively obtained and entered into a logistic 3-level model, with site-specific BoP as the binary outcome variable. The results of the study indicated that (i) the probability for a peri-implant site to be BoP+ significantly increased at the increasing of PD, and was significantly higher in females compared to males and at anterior implants compared to posterior implants; and (ii) BoP manifests similarly around dental implants and contralateral teeth.

In the present cohort of subjects with different conditions of the peri-implant tissues, the prevalence of BoP on a subject-, implant- and site-level was 75.9% (85 patients with at least 1 BoP+ site over 112 patients), 85.7% (246 implants with at least 1 BoP+ site over 287 implants) and 27.9% (478 BoP+ sites over 1713 peri-implant sites), respectively. Data on the prevalence of BoP at the patient- and implant-level were reported in a recent systematic review on the prevalence of peri-implant diseases (Derks & Tomasi 2015). In particular, in studies where BoP was used as a diagnostic parameter for case definition of peri-implant mucositis and peri-implantitis, the prevalence of BoP showed a substantial heterogeneity among studies, ranging between 1% and 65% at the patient-level and between 0.4% and >90% at the implant-level (Derks & Tomasi 2015). On the site-level, a previous study reported a prevalence of BoP around dental implants of 2.78% - 11.56% (depending on the smoking status of the subjects) (de Souza et al. 2012).

Our analysis showed that the probability for a peri-implant site to be BoP+ significantly increased at the increasing of PD, and was significantly higher in females compared to males and in anterior implants compared to posterior implants. Consistent with our findings, the prevalence of BoP at the site level was 9.5% (33 over 347 sites) at sites with PD≤ 3 mm and 66.7% (10 over 15 sites) at sites with PD> 3 mm around implants placed in non-smoker patients (de Souza et al. 2012), and was previously found to be higher in anterior compared to posterior implants, although the difference did not reach statistical significance (Bragger et al. 1997). A recent study on 193 patients with 725 dental implants reported a prevalence of peri-implant disease (identified as the presence of BoP with or without bone loss) of 34.1% and 27% for female and male patients, respectively (Ferreira et al. 2015). At implant-level, a mean BoP score of 0.92 and 0.61 was reported for females and males, respectively (Vered et al. 2011). Overall, these data seem to indicate that females are more prone to manifest bleeding of the peri-implant tissues upon probe stimulation. It may be hypothesized that the influence of hormonal variations on peri-implant tissues in females may reflect that reported for gingival tissues, consisting of a transient increase in the clinical signs of gingival inflammation or the exacerbation of an existing chronic gingivitis despite unvaried levels of plaque (Trombelli & Farina 2013). However, the modulatory effect of hormonal variations on peri-implant mucositis, in general, and BoP, in particular, still needs to be investigated.

The number of covariates was kept limited in order to preserve the power of our multivariate analysis. The reasons for the exclusion of some factors potentially associated with peri-implant BoP are different. The study population showed a highly dispersed distribution according to the configuration of the implant neck/abutment and the type of implant-supported restoration, thus preventing the possibility to compare subgroups of sufficient size. Keratinized tissue width could not be retrieved in a high proportion of the patient record charts. To date, the relationship between keratinized mucosa and peri-implant BoP remains controversial. While recent studies suggest a possible association between BoP and amount of

keratinized mucosa (Romanos et al. 2015, Ueno et al. 2016), previous systematic reviews failed to find a significant association (Lin et al. 2013) or did not retrieve sufficient data to perform an analysis (Gobbato et al. 2013). Data on site-specific plaque levels around dental implants and contralateral teeth could not be retrieved for a number of record charts sufficient to allow for statistical evaluation. The positive relationship between supragingival plaque deposits and severity of supracrestal soft tissue inflammation is well demonstrated around either teeth (Loe et al. 1965, Trombelli et al. 2004, Muller 2009) or dental implants (Pontoriero et al. 1994, Salvi et al. 2012). However, the variability in BoP either among or within individuals can not be merely explained by quantitative nor qualitative differences in plaque accumulation (Abbas et al. 1986, Muller et al. 2000, Trombelli et al. 2004, 2008). In particular, the risk for gingival bleeding in presence of supragingival plaque varies markedly at the subject- and tooth-level (Muller et al. 2000). These findings represented the rationale for the present and previous studies investigating the impact of subject-related and site-specific factors on BoP variability around teeth (Farina et al. 2011, 2013).

Together with findings from our previous study on BoP around teeth (Farina et al. 2013), the present results demonstrated that PD has a strong, positive relationship with BoP probability also around implants. Comparison between teeth and implants showed that, when controlling for PD and other factors influencing BoP (i.e. gender, tooth/implant position), a similar probability for a site to bleed upon probing was found at implant and tooth sites. Moreover, at implant- and tooth-level, a similar distribution pattern according to the number of BoP+ sites was also observed, particularly when BoP+ pockets were analyzed (Table 3). Our results corroborate and expand the findings of previous studies comparing the prevalence of BoP around implants and contralateral teeth. In the study by Vered et al. (2011), mean BoP was 0.77 for implants and 0.85 for contralateral teeth, with no significant differences even when genders were considered separately (Vered et al. 2011). No statistically significant differences in the sulcus bleeding index (and PD) around dental implants and adjacent natural teeth were observed by

Pontoriero et al. (1994) under either real life conditions or following acute, experimentally-induced plaque accumulation. In the study by Bragger et al. (1997), BoP was found at 24% of implant sites and 12% of tooth sites, but this difference was associated with a higher PD at dental implants compared to teeth. Despite the observed differences in probe penetration within the peri-implant/periodontal tissues in different healthy or diseased conditions (Schou et al. 2002, Abrahamsson & Soldini 2006), our findings suggest that BoP manifests similarly around dental implants and contralateral teeth, and the effect of PD seems to account for BoP variability more than the anatomical or patho-physiological characteristics inherent in peri-implant rather than periodontal tissues. For this reason, PD reduction should be regarded as a treatment endpoint to control BoP in prevention and therapeutic strategies of periodontal and peri-implant diseases.

In conclusion, the results of the present study indicated that the probability of a peri-implant site to bleed upon probing is (i) associated with site-specific (i.e. PD, implant position at anterior/posterior sextant) and patient-related factors (i.e. gender), and (ii) similar to that observed at contralateral dental sites when controlling for the effect of PD.

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CONFLICT OF INTEREST

The Authors declare that they have no conflict of interest.

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CONFLICT OF INTERESTS

The Authors have no conflict of interest to declare related to this study.

TABLES

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Table 4. Multivariate model including all factors (i.e., gender, PD, and implant position) with a significant impact on the probability of a peri-implant site to be BoP+. The model is based on data from 1725 peri-implant sites in 289 implants placed in 112 patients.

FIGURE LEGEND

Figure 1. Patient selection: flow chart.

Figure 2. Predicted mean probability of a peri-implant site to be positive to bleeding on probing (Prob BoP+) according to its probing depth (PD).

Figure 3. Predicted probability for a peri-implant site to be BoP+ (P(BoP+)) according to gender, probing depth (PD), and implant position.

Table 1. Study population.

	n	mean (SD)	range
patients	112		
number of teeth present		21.9 (5.6)	3 - 31
number of implants present		2.6 (2.2)	1 – 16
age		55.2 (12.1)	22 - 81
gender (males/females)	53 / 59		
smokers (current smoker / former smoker / never smoked)	28 / 15 / 69		
cigarettes/day		12.3 (7.5)	2 - 30
years of smoking		26.1 (10.0)	10 - 50
diabetes (1 or 2)	4		

Table 2. Mean characteristics of dental implants included for analysis.

	Implants
number	289
arch (% maxillary / % mandibular)	54% / 46%
location (% anterior / % posterior)	26% / 74%
% of BoP+ sites mean (SD) range (minimum - maximum)	27.6 (29.3) 0 - 100
PD mean (SD) range (minimum - maximum)	3.5 (1.1) 1.3 - 7.5
prosthesis (% single crowns / % bridges / % removable)	48% / 41% / 11%

Table 3. Distribution of implants and contralateral teeth according to the number of BoP+ sites per tooth/implant, as calculated either irrespective of PD or associated with PD≥ 5 mm.

number of BoP+ sites	all implants (n= 289)		implants with a contralateral tooth (n= 170)		contralateral teeth (n= 170)	
	n	%	n	%	n	%
0	105	36.3	70	41.2	67	39.4
1	60	20.8	37	21.8	37	21.8
2	37	12.8	19	11.2	19	11.2
3	44	15.2	22	12.9	27	15.9
4	17	5.9	13	7.6	12	7.1
5	12	4.2	6	3.5	6	3.5
6	14	4.8	3	1.8	2	1.2
number of BoP+ sites associated with PD≥ 5 mm	**all implants (n= 289)**		**implants with a contralateral tooth (n= 170)**		**contralateral teeth (n= 170)**	
	n	%	n	%	n	%
0	210	72.7	129	75.9	132	77.6
1	38	13.1	16	9.4	26	15.3
2	15	5.2	13	7.6	3	1.8
3	11	3.8	6	3.5	9	5.3
4	13	4.5	6	3.5	0	0
5	2	0.7	0	0	0	0
6	0	0	0	0	0	0

Table 4. Multivariate model including all factors (i.e., gender, PD, and implant position) with a significant impact on the probability of a peri-implant site to be BoP+. The model is based on data from 1725 peri-implant sites in 289 implants placed in 112 patients.

Outcome: BoP (+/-)	Parameter	Standard Error	OR	95% CI	p value
Fixed Part					
intercept	-0.80	0.24			
PPD (centered 4 mm)	0.47	0.06	1.59	1.43 – 1.77	<0.001
females versus males	0.47	0.24	1.61	1.00 – 2.57	0.048
posterior versus anterior	-0.61	0.22	0.55	0.36 – 0.83	< 0.01
Random Part					
patient level variance	0.61	0.21			
tooth level variance	0.76	0.19			

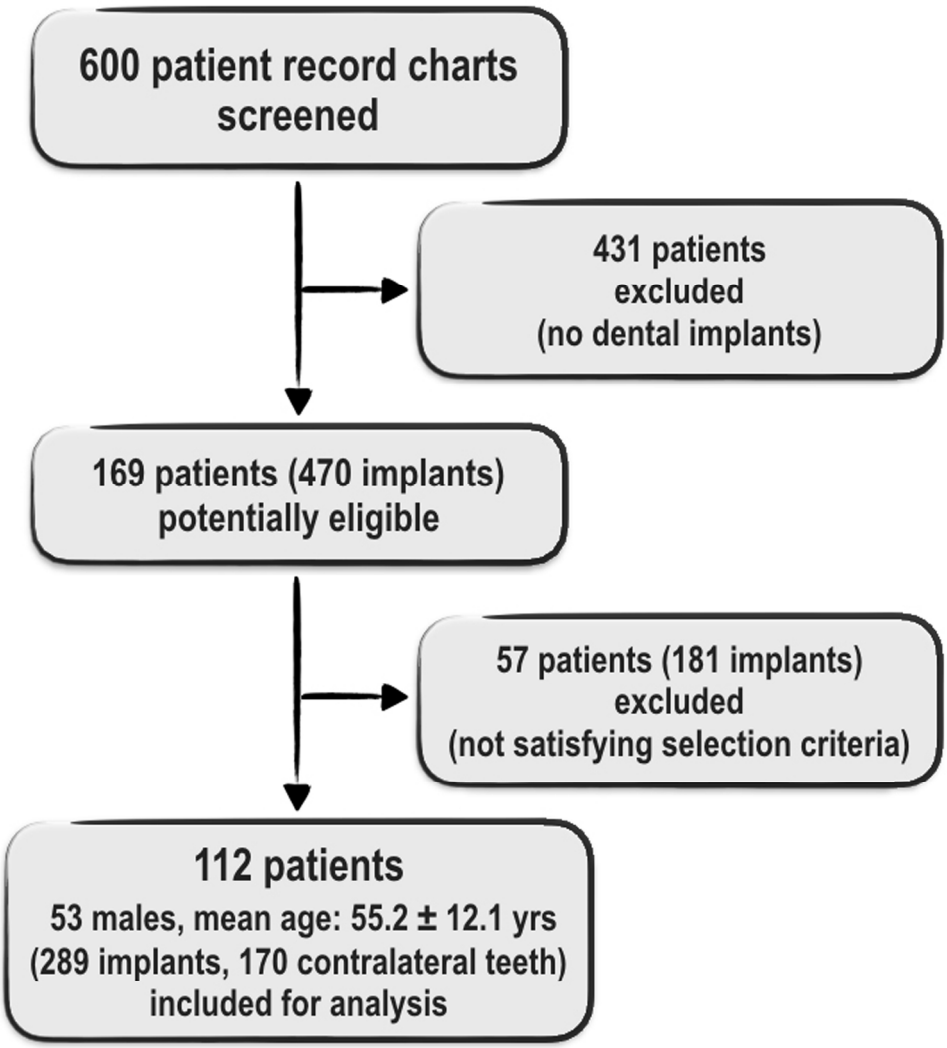

Figure 1: Patient selection: flow chart.
Figure 1
250x274mm (300 x 300 DPI)

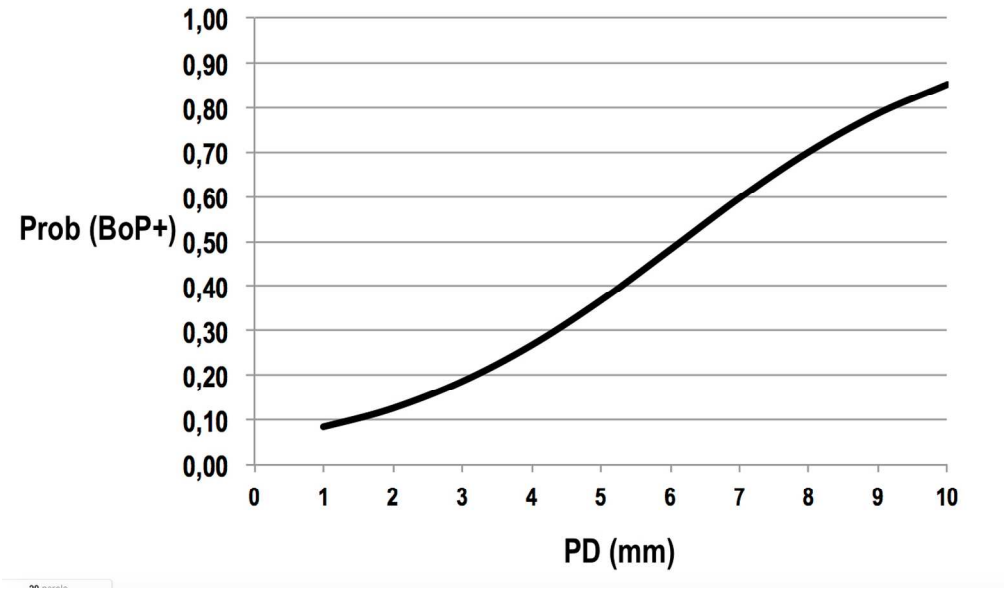

Figure 2: Predicted mean probability of a peri-implant site to be positive to bleeding on probing (Prob BoP+) according to its probing depth (PD).
Figure 2
477x282mm (300 x 300 DPI)

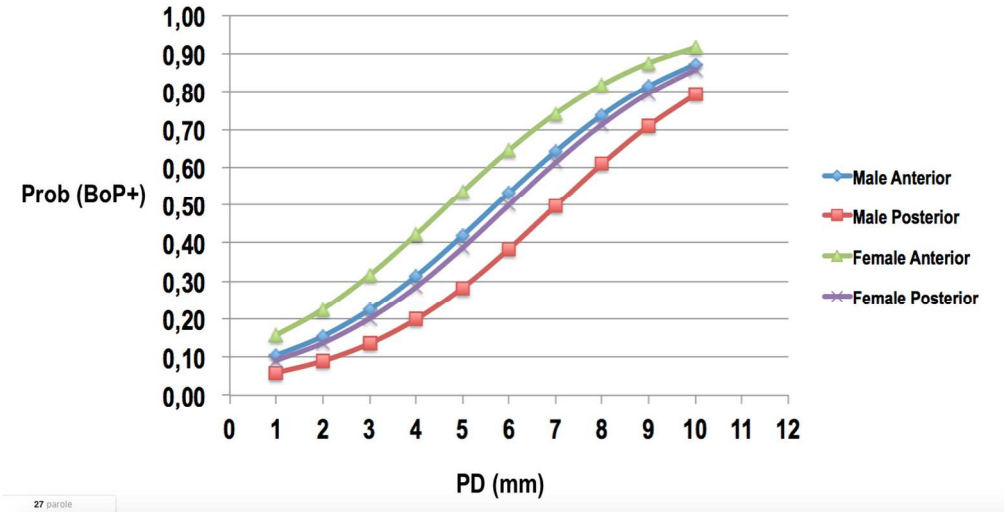

Figure 3: Predicted probability for a peri-implant site to be BoP+ (P(BoP+)) according to gender, probing depth (PD), and implant position.
Figure 3
482x252mm (300 x 300 DPI)