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ORIGINAL ARTICLE

Sexual dimorphism in periodontal inflammation: A cross-sectional study

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Abstract

Background: The purpose of the present study was to evaluate the role of sexual dimorphism (SD) in the clinical manifestation of plaque-induced periodontal inflammation by analyzing the association between patient-related factors and the full-mouth prevalence of bleeding on probing (BOP%) within 2 cohorts of male and female individuals.

Methods: Data on BOP (dichotomously recorded as present/absent after the assessment of probing depth [PD]) were retrospectively obtained from the files of adult patients undergoing a first periodontal visit at a University center. Two multiple regression models (1 for males, 1 for females) were built with BOP% as the dependent variable and patient-related factors (i.e., age; smoking status; daily cigarette consumption; history of diabetes diagnosis; number of teeth present; proportion of sites with PD ≥ 5 mm around teeth) as independent variables.

Results: In males ($n = 212$), BOP% was 5.9% lower in smokers compared to non-smokers ($p = 0.021$). In females ($n = 389$), BOP% increased by 1.6% for each 10-year increase in age ($p = 0.046$). The proportion of sites with PD ≥ 5 mm showed a strongly significant, positive association with BOP% irrespective of biological sex ($p < 0.001$).

Conclusion: SD manifested as a sex-dependent diversity in the association between patient-related factors and periodontal inflammation expressed as BOP%. While smoking determined a lower BOP% only in males, aging was associated with increased BOP% only in females.

KEYWORDS
gingival hemorrhage, gingival pocket, inflammation, periodontal pocket, sex

Plain Language Summary

Gingival bleeding upon mechanical stimulation of the bottom of the gingival sulcus/pocket with a periodontal probe (bleeding on probing [BOP]) is

suggestive of the presence of an inflammatory infiltrate induced by dental plaque within the gingival tissue. The prevalence of BOP within the dentition (BOP%) has a diagnostic relevance, being one of the main parameters to discriminate between periodontal health and disease. Also, BOP% informs the probability for a patient to either develop destructive form of periodontal disease (i.e., periodontitis) or manifest periodontitis progression. Based on the documented influence of biological sex on the incidence, traits, and/or progression rate of several diseases, which goes under the name of sexual dimorphism (SD), the effect of SD was investigated in relation to the factors that were previously associated with BOP% in a cohort of patients with heterogeneous periodontal conditions undergoing their first periodontal visit. Interestingly, SD manifested as a sex-dependent diversity in the association between patient-related factors and periodontal inflammation expressed by BOP%. While smoking determined a lower BOP% only in males, aging was associated with increased BOP% only in females. The present findings may find potential applications in personalized periodontal medicine and inspire future studies in this field.

1 | INTRODUCTION

Biological sex differentially regulates the expression of several traits related to sex chromosomes but also autosomes[1–7] and determines different expressions of the endocrine,[8–10] immune,[11–14] and other systems. Under this principle, disease risk factors may differ between sexes, leading to disease incidence, traits, and/or progression rate variations. Due to the significance of sexual dimorphism (SD), the importance of biological sex as a critical methodological element in the biomedical sciences has recently emphasized.[15–17]

Evidence supports the relevance of SD in the pathophysiology of plaque-induced periodontal diseases. In a gene-sex interaction study on early-onset periodontitis, 20 genetic loci were identified, carrying specific alleles that modify periodontitis incidence and traits in interaction with sex. In women, most of the prevalent variants of the investigated single nucleotide polymorphisms had been previously associated with increased disease risk.[18] On the physiological side, females were also shown to have a higher incidence of gingival cell apoptosis, with potential consequences in the clearance of inflammatory cells and tissue healing,[19] and a different gingival expression of specific cytokines (e.g., higher IL-17A expression) with aging[20] when compared to males. On the other hand, better migration ability and propensity to induce an enrichment of the inflammatory infiltrate with greater amounts of specific osteoclast precursors was reported for neutrophils of males compared to females.[21]

Given the above, it is plausible to hypothesize that SD may become manifest when evaluating the well-documented influence of factors such as deep pockets,[22] diabetes,[23,24] smoking,[25–27] and aging[22,28–32] on clinical measures of periodontal inflammation, including bleeding on probing (BOP). In this respect, an exclusive association of BOP with single and combined components of the metabolic syndrome has been recently reported for females,[33] thus corroborating this hypothesis and supporting the need for further studies on the relevance of biological sex and SD in periodontal medicine in general, and periodontal inflammation, in particular.

The aim of the present study was to evaluate the relevance of SD in the clinical manifestation of periodontal inflammation by evaluating the association between subject-related factors and the prevalence of BOP in the whole dentition separately in male and female individuals.

2 | MATERIALS AND METHODS

2.1 | Experimental design

Data from the study by Farina et al.[22] were reanalyzed for the present cross-sectional study.

2.2 | Study population

All 601 patients participating in the study by Farina et al.[22] contributed the present analysis. Briefly, adult, dentate, or

partially edentulous patients underwent an initial (first) periodontal visit within a 10-year period (1996–2006) at the Research Center for the Study of Periodontal and Peri-Implant Diseases, University of Ferrara, Italy, and presented conditions varying between plaque-induced gingivitis to advanced periodontitis. Patients were excluded from the analysis if positive for at least 1 of the following criteria: periodontal treatment received within the last 6 months prior to visit; pregnancy or lactation; less than 15 teeth present; presence of dental implants; orthodontic appliances; genetic defects (e.g., Down syndrome) with an established impact on periodontal status; immune system disorders (e.g., HIV/AIDS); severe blood disorders, with a documented qualitative and/or quantitative deficit of polymorphonuclears and/or platelets; physical or mental illness that can interfere with adequate oral hygiene performance; assumption of anti-aggregants or anti-coagulants; assumption of medications affecting the gingiva and/or the oral mucosa (e.g., diphenylhydantoin, calcium channel blockers, cyclosporin A, immunostimulants/immunomodulators).

Information on biological sex (recorded as "male" or "female") was extracted from the patient record chart, which in turn reported information found in the identity document used for patient registration at first visit.

2.3 | BOP assessment and full-mouth prevalence

At site-level, BOP was dichotomously recorded as present/absent after the assessment of probing depth (PD).[34] Probing was performed by 4 trained examiners with long-term expertise in periodontal research using a manual periodontal probe* at a probing force of about 0.2 N. At subject-level, the prevalence of BOP was expressed as full-mouth percentage proportion (%) of BOP-positive sites (BOP%).[34]

2.4 | Factors evaluated for their association with BOP% within each sex cohort

Within each sex cohort, the inter-subject variability in BOP% was evaluated according to the following patient-related factors:

1. Age;
2. Smoking status: recorded as current smoker or non-smoker[22];
3. Number of cigarettes smoked per day (1–9, 10–19, or ≥20 cigarettes/day);
4. History of diabetes diagnosis (diabetic, non-diabetic);
5. Number of teeth present;
6. Percentage proportion of tooth sites with PD ≥ 5 mm.

2.5 | Statistical analysis

The patient was the statistical unit for analysis. Within each cohort, data was expressed as mean, standard deviation (SD), and minimum-maximum range for continuous variables and frequency analysis for categorical variables. Two multiple regression models (1 for males, 1 for females) were built with BOP% as the dependent variable; the statistical significance of each independent variable for BOP variability was evaluated with the Wald test. For clearer interpretation of the regression data, age was transformed into a categorical variable with 10-year steps until 80 years and up. Moreover, for age, the intercept was calculated, centering age on 40 years. A statistical software† was used for the analysis. The level of statistical significance was fixed at 5%.

3 | RESULTS

3.1 | Study population

A total of 212 males and 389 females contributed the present analysis. The patient-related characteristics of each cohort are reported in Table 1.

3.2 | Factors associated with BOP% in males

In males, BOP% was associated with the percentage of sites with PD≥ 5 mm ($p < 0.001$) and smoking status ($p = 0.021$) (Table 2). The model explained 30.9% of BOP% variability ($R^2 = 0.309$). On average, smokers showed 5.9% lower BOP% compared to non-smokers. However, the effect was not significantly dependent on the daily cigarette consumption. A 10% increase in the percentage of sites with PD≥ 5 mm was paralleled by an increase of 6.1% in BOP% (Figure 1).

3.3 | Factors associated with BOP% in females

In females, BOP% was associated with the percentage of sites with PD≥ 5 mm ($p < 0.001$) and age ($p = 0.046$) (Table 2). The model explained 32.6% of BOP% variability

* CP12; Hu-Friedy, Chicago, Illinois, US.

† SPSS 24; IBM, Segrate (Milan), Italy.

TABLE 1 Patient characteristics of male and female cohorts.

Parameter	Males ($n = 212$)	Females ($n = 389$)
BOP%		
mean (± SD; min-max range)	28.7% (± 20.1%; 0%–100%)	28.8% (± 18.0%; 0%–83.3%)
Age (years)		
mean (± SD; min-max range)	46.8 (± 11.2; 21–77)	44.0 (± 11.2; 20–76)
Prevalence of smokers		
n (%)	69 (32.6%)	107 (27.5%)
Daily cigarette consumption		
1–9 cigarettes/day	21 (30.0%)	34 (31.7%)
10–19 cigarettes/day	18 (26.1%)	42 (39.3%)
≥20 cigarettes/day	30 (43.9%)	31 (29.0%)
n (%)		
Prevalence of diabetics		
n (%)	9 (4.2%)	10 (2.6%)
No. of teeth present		
mean *n* (± SD; min-max range)	25.8 (± 3.9; 15–32)	25.7 (± 3.5; 15–32)
Proportion of sites with PD≥ 5 mm		
mean % (± SD; min-max range)	18.4% (± 16.9%; 0%–73.1%)	14.0% (± 14.7%; 0%–85.6%)

Abbreviations: BOP, bleeding on probing; PD, probing depth; SD, standard deviation.

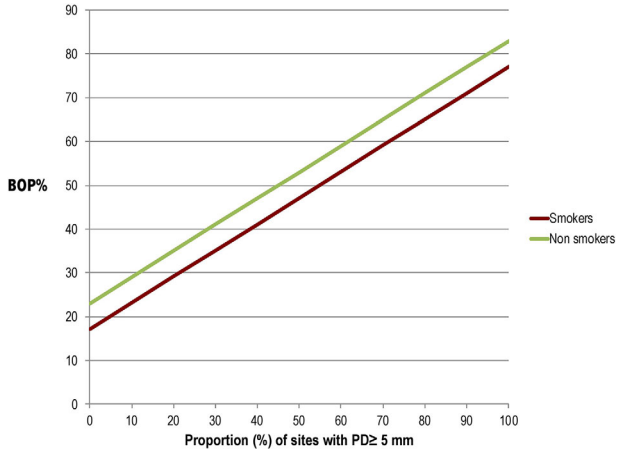

FIGURE 1 Predicted BOP% in male cohort as stratified according to significant BOP% determinants (i.e., smoking status and proportion of sites with PD≥ 5 mm). BOP%, bleeding on probing; PD, probing depth

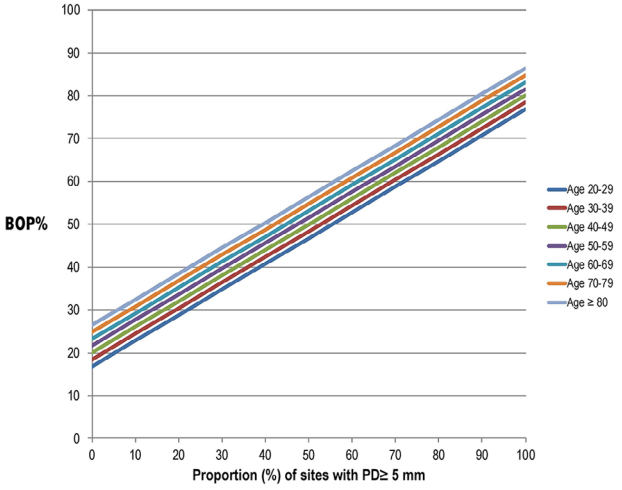

FIGURE 2 Predicted BOP% in female cohort as stratified according to significant BOP% determinants (i.e., age and proportion of sites with PD≥ 5 mm). BOP%, bleeding on probing; PD, probing depth

($R^2 = 0.326$). On average, BOP% increased by 1.6% for each 10-year increase in age, and by 5.6% for each 10% increase in the percentage of sites with PD ≥ 5 mm (Figure 2).

4 | DISCUSSION

The present cross-sectional study was performed to evaluate the influence of SD on periodontal inflammation (expressed as the full-mouth BOP prevalence, BOP%). Interestingly, smoking and age were differentially associated with BOP% according to the patient sex, with smoking determining a lower BOP% in males while aging being associated with increased BOP% in females. These findings corroborate the relevance of SD in determining the phenotype of chronic inflammatory diseases, as previously reported in the context of either periodontal diseases[33] or other inflammatory, non-communicable diseases such as rheumatoid arthritis,[35,36] diabetes,[37,38] cardiovascular disease,[10,39–43] and gut diseases,[44] and reinforce the

TABLE 2 Results of the multivariate analysis evaluating the association between BOP% (dependent variable) and candidate factors within each sex cohort

	BOP% males							BOP% females						
			95% Wald CI		Hypothesis test					95% Wald CI		Hypothesis test		
Parameter	B	Std error	Lower	Upper	Wald chi-square	df	*p*-value	B	Std error	Lower	Upper	Wald chi-square	df	*p*-value
Intercept	23.105	3.4876	16.269	29.940	43.887	1	<0.001	19.896	2.0687	15.842	23.951	92.500	1	<0.001
Smoking status (ref: smokers)	−5.873	2.5524	−10.876	−.870	5.294	1	0.021	−1.720	1.8971	−5.438	1.999	.822	1	0.365
Diabetes (ref: diabetics)	7.585	5.7443	−3.673	18.844	1.744	1	0.187	6.611	5.2126	−3.605	16.828	1.609	1	0.205
Age (ref: 40 years; 10-year increments)	−1.674	1.2347	−4.094	.746	1.837	1	0.175	1.637	.8218	.026	3.248	3.968	1	0.046
Proportion (%) of sites with PD≥ 5 mm	.612	.0722	.470	.753	71.874	1	<0.001	.563	.0577	.450	.676	95.097	1	<0.001
No. of teeth (centered at 20 teeth)	−.506	.3561	−1.204	.192	2.020	1	0.155	.111	.2603	−.400	.621	.181	1	0.671
Scale	282.766[c]	27.464	233.75	342.06				254.086[c]	18.218	220.77	292.46			

Abbreviations: BOP, bleeding on probing; CI, confidence interval; PD, probing depth.

relevance of biological sex as a variable in periodontal research.[45]

Through a series of local and systemic effects, smoking exerts a well-documented, suppressive effect on the gingival bleeding response,[46–51] which is independent of quantitative and qualitative differences in plaque deposits.[46,49] Interestingly, in the present study, such effect was found (statistically significant, although limited in magnitude) only in males, with non-smokers showing 5.9% higher BOP% compared to smokers. This finding is supported by the results of a previous study where a significant association between cigarette smoking and systemic inflammation (expressed in terms of C-reactive protein levels) was observed in men, but not in women.[52] Although differences in sex hormone types and levels[53] and puffing behavior (with women taking smaller and shorter puffs compared to men[54]) may contribute this difference, the reason for the sex-specific effect of smoking on inflammation remains largely unexplained. The suppressive effect of smoking on BOP as observed in our male cohort may appear in contrast with the increases in the blood levels of pro-inflammatory mediators that accompany smoking exposure (even for short periods) and were found to be particularly marked in male individuals.[55,56] However, it must also be considered that smoking also leads to decrements in gonadal hormones in both sexes.[55,56] When considering that a positive correlation between testosterone levels and the severity of gingival inflammation has been reported,[57] our findings may indicate that the immune suppression due to the decrease in testosterone levels associated with chronic smoking exposure prevails on the testosterone-associated increase in cytokine production and its sequelae on gingival inflammation. Future studies will allow for verifying this hypothesis and further clarifying the relationship between the relevance of the dose-dependent effect of smoking, which was not found in our male cohort in contrast with previous observations.[26,52]

In the present material, BOP% showed small but significant 1.6% increases for each 10-year increase in the age of females, while it was not significantly influenced by age in males. This finding is supported by previous experimental gingivitis studies, which elegantly demonstrated that older subjects developed a more rapid and severe plaque-induced gingival inflammatory response compared to younger subjects,[28,58] with the effect of aging being independent of quantitative aspects of supragingival plaque accumulation.[28] Also, no major differences in the subgingival periodontal microbiota were found between older and younger adults, especially in the absence of destructive periodontal disease.[59] The inverse relationship between age and bleeding was not clinically marked (50 additional years of age would result in 10% lower BOP), statistically independent of the proportion of periodontal pockets (which commonly increase with age), and was observed only in females. Some potential explanations can be advanced for the latter association. Although both sexes experience age-associated reductions in sex hormones,[60–63] a bi-potential role of estrogens has been reported, with events occurring early in life (e.g., menstrual cycle, pregnancy) being associated with high estrogen doses leading to decreased inflammatory cytokine production.[64] The observed results also leave space for a potential role of sex-related differences in inflammaging[29,30] and its key cellular mechanisms, including immunosenescence, and the tissue amassing of proinflammatory cells with aging.[65] At the end of the reproductive period, the immune system of females partly loses its efficiency,[66] and alterations in the functions of immune cells and more marked immunosenescence were shown to parallel the decrease in estrogen production that follows menopause.[65]

According to the present analysis, the strong, positive association between PD and BOP previously reported at both site-[50,67,68] and patient-level[22] remained strongly significant when male and female cohorts were considered separately. Specifically, the BOP score increased by 6.1% and 5.6% in males and females, respectively, for each 10% increase in the percentage of sites with PD≥ 5 mm. Considering this information, it is plausible that PD effect on BOP (see Figure S1 in online *Journal of Periodontology*) may be so potent to mask any sex-based differences (if any). The present findings also support the universal (i.e., without sex-specific personalization) use of PD and BOP as the endpoints of periodontitis therapy, as currently reported in the EFP S3 Guidelines.[69]

Some shortcomings of the study should be considered when interpreting the present findings. First, the candidate determinants introduced into the statistical models explained about one-third of BOP% variability in both male and female cohorts, with two-thirds remaining currently unexplained. Supragingival plaque could not be included among candidate determinants due to the unavailability of data in the patient record charts. For some independent variables that were included in our analysis such as smoking and diabetes, the lack of some information (e.g., duration of the smoking habit, time from diabetes diagnosis, level of metabolic control of diabetic patients) has probably limited the possibility to fully capture their effect (if any) within each sex cohort. Also, some candidate determinants (e.g., diabetes) were probably underrepresented in both study cohorts. While the present analysis focused on the role of sex biology, future work would need to focus on the socio-behavioral, cultural/traditional, and environmental aspects associated with gender. These constructs affect access to health care,[70,71] psychosocial stress,[72,73] oral hygiene habits,[74–76] and diet[77,78] and may contribute

to disease phenotypic presentation.[64] Although the integration of information related to sex and gender would have significantly helped to clarify the complex interaction between biological and socio-behavioral dimensions in determining BOP% variability, the retrospective nature of the study precluded the collection of any information related to gender.

Collectively, the present results showed that SD manifests as a sex-dependent diversity in the effect of patient-related factors on periodontal inflammation, expressed as BOP%. While smoking determined a lower BOP% only in males, aging was associated with increased BOP% only in females. Differently, the proportion of periodontal pockets showed a strong, positive association with BOP% irrespective of biological sex.

AUTHOR CONTRIBUTIONS

Roberto Farina and Leonardo Trombelli conceived the research question and designed the study. Cristiano Tomasi analyzed the data and generated the figures. Roberto Farina and Anna Simonelli took the lead in drafting the manuscript. Roberto Farina, Anna Simonelli, Cristiano Tomasi, and Leonardo Trombelli aided in interpreting the results. Effie Ioannidou and Leonardo Trombelli provided valuable criticism to the final version of the manuscript. All authors gave their final approval and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Access to all data will be shared upon reasonable request (roberto.farina@unife.it).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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