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ORIGINAL ARTICLE

Hematological features in adolescents with periodontitis

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Abstract The aim of this study was to assess whether adolescent cases of periodontitis present with different hemogram findings than control subjects. This case–control study comprised 87 adolescent cases presenting with clinical attachment loss ≥3 mm in at least two teeth and 73 control subjects. Blood samples were obtained by venipuncture and analyzed in an Abbott Cell-Dyn 3,500 hematology analyzer for values of white blood cells and red blood cells, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red-cell distribution width, platelets, and mean platelet volume. Hematocrit values were obtained using volume fractions read from capillary tubes. The associations between log-transformed hemogram variables with each of the three exposure variables "case status" (yes/no), a "high percent sites with PD ≥4 mm" (yes/no), and a "high percent sites with BOP" (yes/no) were investigated using multivariate linear regression analyses. Periodontitis cases presented with 5% higher values for the mean platelet volume than did controls. Subjects with a high percent sites with probing depth ≥4 mm had eosinophil counts that were on average 27% lower than among subjects with fewer deepened pockets. They also had 7% higher values for the mean platelet volume than did persons with less pocketing. Eosinophil counts and mean platelet volumes may be associated with the parameters of periodontitis in adolescents. While standard hematological testing did not show abnormalities in adolescents with periodontitis compared to healthy controls, eosinophil counts and mean platelet volumes may reflect periodontal inflammation.

Keywords Adolescents · Blood cells · Blood platelets · Hematocrit · Hematologic tests · Hemoglobin · Periodontitis

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Introduction

The results of several studies in the periodontal literature suggest that adult patients with periodontitis frequently present with significant differences in blood parameters when compared to healthy controls[1–5], and while the values for the different blood parameters investigated often do not exceed the reference values used in the clinic [6], the literature is consistent that periodontitis patients do have elevated systemic markers of inflammation when they are compared to subjects without periodontitis [6].

If these reported differences reflect the effect of periodontal inflammation, it could be expected that differences in blood parameters between subjects with and without periodontitis are even more pronounced among young subjects. Hence, adults are more likely to have been exposed to concurrent inflammatory conditions and other influential factors such as smoking than are young subjects,

and a comparison between young cases of periodontitis and healthy controls will therefore be less influenced by the noise from such confounding factors.

To the best of our knowledge, only one study has attempted to compare the general hematological values for adolescents according to their periodontal status and the authors only considered subjects with periodontitis, i.e., juvenile periodontitis and chronic periodontitis [7]. The results of that study did not indicate the existence of differences between subjects in these disease categories [7], but the question whether young subjects with periodontitis present with hematological values that are different from that of healthy subjects remains unanswered. Thus, it seems natural to acquire more knowledge for young periodontitis cases on standard hematological factors using common laboratory tests. The aim of this study was to assess whether adolescents with periodontitis present with different laboratory findings on blood parameters when compared to controls originating from the same underlying population.

Materials and methods

The study group considered in this analysis comprised 87 adolescent cases of periodontitis presenting with clinical attachment level (CAL) ≥3 mm in at least two of 16 teeth recorded and 73 healthy subjects who did not fulfill these criteria (controls). In order to avoid misclassification due to gingival recession after orthodontic treatment, we excluded canines and premolars from the subset of teeth examined in the screening. More detailed analyses on the distribution of periodontal parameters in this study group show that the largest burden of attachment loss and pocketing was found in molars and incisors which only very rarely present with gingival retraction after orthodontic treatment [8]. All subjects were nested in a well-defined adolescent population (N=9,162) that had been selected using a multi-stage random sampling procedure and screened for signs of periodontal destruction [9, 10]. The target population included all students attending the four high school grades covering adolescence in the Province of Santiago, Chile.

The case–control study was conducted during a 3-month period starting in September 2000. Details on the sampling strategy, sample size estimations, participation rates, clinical recordings used to identify the cases, intra- and inter-examiner reliability in the recording of CAL, and a detailed description of the clinical periodontal features of cases and controls have been previously published [8, 9, 11, 12]. Ethical approval for the study was obtained from the Ethics Committee of the University of Chile, and informed written consent was provided by each participant or their parents, as appropriate.

Clinical examinations

The case–control study was conducted during a 3-month period. All examinations were conducted during a single visit. The participants were asked to answer a set of questionnaires, then they received a clinical dental examination, and finally blood samples were obtained. A trained and calibrated periodontist (RL) who was blinded for case status conducted complete periodontal examinations, which included direct recordings of CAL, probing pocket depth (PD), bleeding on probing (BOP), and supragingival plaque and calculus at six sites per tooth for all teeth present, excluding third molars [8]. The occurrence of bleeding on probing, supragingival plaque, and supragingival calculus were recorded as dichotomous variables (yes/no). Bleeding on probing was recorded 15 s after the assessment of PD. It is inevitable that some measurement variation occurs in any kind of repeated recording. In order to preserve the validity of the case–control study design, we maintained the subjects in the group to which they were initially allocated according to the screening for clinical attachment, irrespective of the results of the case–control examinations.

Blood sampling

A total of 3 mL of non-fasting blood was obtained by venipuncture from each participating subject using BD Vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) with anticoagulant (EDTA). Samples were immediately transferred to a technician who was blinded for case status. Blood samples were processed and analyzed according to manufacturer's instruction in a calibrated Abbott Cell-Dyn 3,500 automated hematology analyzer (Abbott Laboratories, IL, USA) for hemogram values, i.e., leukocyte counts ($10^3/\mu L$), neutrophils ($10^3/\mu L$), eosinophils ($10^3/\mu L$), basophils ($10^3/\mu L$) ($\times 10^{-2}$), lymphocytes ($10^3/\mu L$), monocytes ($10^3/\mu L$), red blood cells ($10^6/\mu L$), hemoglobin (g/dL), mean corpuscular volume (fL), mean corpuscular hemoglobin (pg/cell), mean corpuscular hemoglobin concentration (g/dL), red-cell distribution width (%), platelets ($10^3/\mu L$), and mean platelet volume (fL). To obtain the hematocrit values, a capillary tube was filled and centrifuged at 10,000 rpm for 5 min and the values for the volume fraction were transferred to a scale table.

Statistical analysis

Differences in the hemogram values between cases and controls were statistically tested using the Mann–Whitney U test, and p values were reported. Fisher's exact test was used to assess whether cases presented with significantly different values from the reference values when compared to the control subjects.

All hemogram variables were log-transformed before multivariate linear regression analyses (regress command in STATA 11.0) of their association with each of the three exposure variables case status (yes/no), a high percent sites with PD ≥4 mm (yes/no), and a high percent sites with BOP (yes/no) were carried out. A high percent sites was defined by values at or above the median value for the entire study group, whereas a low percent sites was defined by values below the median. The logarithmic transformation of the hemogram variables was employed to remove positive skewness and to make standard deviations more similar across the range of hemogram values. Linear regression analysis of log-transformed data implies that a multiplicative, rather than additive, regression model is used. This means that the estimated regression coefficients have a multiplicative interpretation. As an example, a coefficient value of 1.10 for cases means that cases have 10% higher value of the untransformed outcome variable than do controls. All multivariate linear regression models were adjusted for age (continuous), gender, and daily smoking (yes/no), and these adjustment variables were retained in the model if $p<0.20$. Multicollinearity between covariates was evaluated for each regression model by assessing the variance–covariance matrix (vce command in STATA 11.0). The appropriateness of applying linear regression models to the data was finally evaluated by examining graphical plots of the residuals versus the fitted values.

Results

Cases and controls were of comparable age and the occurrence of daily smoking was similar for both groups (Table 1). There were more girls among the cases than among the controls, but this difference did not reach statistical significance. All cases and 87.7% of the controls presented with CAL ≥1 mm, but the average percent sites with CAL ≥1 mm was substantially higher among cases than among controls (21.2% vs. 3.6%) (Table 1). Pocket depths ≥4 mm were also more common (88.5% vs. 45.2%) and more widespread (mean percent sites affected 5.3% vs. 1.2%) among cases than among controls (Table 1). The occurrence of BOP was similarly high among cases and controls, but cases had a significantly higher mean percentage of sites affected than controls (44.6% vs. 13.6%) (Table 1).

The bivariate statistical analyses showed only one statistically significant difference in the hemogram values between cases and controls (Table 2); cases had higher values of the mean platelet volume than did controls.

The distribution of values with respect to the recommended reference values for the different hematological parameters was similar for cases and controls (data not shown).

The values for white blood cells ranged from 4.0 to 17.6×10^3/μL for control subjects and from 4.2 to 15.4×10^3/μL for the cases (Appendix). The corresponding values for neutrophils ranged between 2 and 12.8 for controls and 1.3 to 10.0 for the cases (Appendix). The values for red blood cells ranged between 3.9 and 6.0 for controls and from 3.7 to 5.8 for cases (Appendix). There were no significant differences between cases and controls for any of these parameters.

The results of the multiple linear regression analyses of the association between the hemogram values and any of the three periodontal exposure variables (case status, a high percent sites with probing depth ≥4 mm, or a high percent sites with BOP) showed statistically significant lower eosinophil counts and a high percent sites with probing depth ≥4 mm (Table 3).

Table 1 Demographic and clinical characteristics of cases and controls

	Cases (n=87)	Controls (n=73)	p value
Age, years (mean/age range)	16.7/13–20	16.4/13–19	0.097[a]
Females (%)	62.1%	46.6%	0.050[b]
Daily smokers (%)	25.3%	24.7%	0.927[b]
% persons having lost ≥1 teeth	43.7%	35.6%	0.300[b]
% persons with CAL ≥1 mm	100%	87.7%	0.001[b]
% persons with CAL ≥3 mm	97.7%	11.0%	0.000[b]
% persons with PD ≥4 mm	88.5%	45.2%	0.000[b]
% persons with PD ≥5 mm	49.4%	12.3%	0.000[b]
% persons with BOP	100%	97.3%	0.120[b]
Mean no. of teeth lost	0.44	0.36	0.303[a]
Mean % sites with CAL ≥1 mm per person	21.2	3.6	0.000[a]
Mean % sites with CAL ≥3 mm per person	4.1	0.2	0.000[a]
Mean % sites with PD ≥4 mm per person	5.3	1.2	0.000[a]
Mean % sites with PD ≥5 mm per person	1.4	0.2	0.003[a]
Mean % sites with BOP per person	44.6	13.6	0.000[a]

CAL clinical attachment level, *PD* probing depth, *BOP* bleeding on probing

[a] *t* test

[b] Chi square

Table 2 Mean, median, and 75% percentile values for the hemogram parameters according to periodontal case-status

		Cases (n=87)			Controls (n=73)			
		Mean±SD	Median	75% percentiles	Mean±SD	Median	75% percentiles	p value[a]
WBC		7.61±1.94	7.20	8.56	7.23±2.20	6.68	8.35	0.084
	NEU	4.60±1.71	4.35	5.43	4.27 ±1.83	3.87	5.00	0.083
	LYM	2.21±0.64	2.15	2.58	2.20±0.52	2.18	2.51	0.995
	MONO	0.53±0.14	0.51	0.61	0.51±0.15	0.48	0.59	0.221
	EOS	0.21±0.50	0.10	0.22	0.20±0.17	0.16	0.25	0.156
	BASO	0.06±0.03	0.06	0.08	0.06±0.02	0.06	0.07	0.928
RBC		4.75±0.41	4.78	5.04	4.84±0.46	4.83	5.14	0.295
	HGB	14.04±1.18	14.00	14.9	14.40±1.32	14.30	15.30	0.096
	HCT	41.00±3.48	41.00	43.30	41.87±3.81	41.80	44.90	0.165
	MCV	86.39±3.93	86.40	88.90	86.65±3.34	86.80	88.40	0.847
	MCH	29.61±1.50	29.70	30.60	29.80±1.30	29.80	30.50	0.657
	MCHC	34.27±0.56	34.20	34.60	34.39±0.53	34.40	34.70	0.158
	RDW	14.40±0.87	14.40	15.00	14.38±0.83	14.30	15.00	0.887
PLT		263.01±55.72	261	334	271.59±50.87	273	303	0.248
	MPV	8.76±1.21	8.59	9.26	8.37±1.55	8.15	8.96	0.011

WBC leukocyte count, *NEU* neutrophils, *EOS* eosinophils (10^3/μL), *BASO* basophils (10^3/μL) ($\times 10^{-2}$), *LYM* lymphocytes, *MONO* monocytes (10^3/μL), *RBC* red blood cells (10^6/μL), *HTC* hematocrit (%), *HGB* hemoglobin (g/dL), *MCV* mean corpuscular volume (fL), *MCH* mean corpuscular hemoglobin (pg/cell), *MCHC* mean corpuscular hemoglobin concentration (g/dL), *RDW* Red-cell distribution width (%), *PLT* platelets (10^3/μL), *MPV* mean platelet volume (fL)

[a] Mann–Whitney *U* test

The analysis showed that subjects with a high percent sites with probing depth ≥4 mm had eosinophil counts that were on average 27% lower than among subjects with fewer deepened pockets (Table 3). Although subjects presenting with a high percent sites with bleeding on probing had an average of 24% lower eosinophil counts than did subject with less bleeding (Table 3), this difference was barely significant at p=0.05.

Case subjects presented with values for the mean platelet volume that were on average 5% higher than seen among controls. Subjects with a high percent sites with probing depth ≥4 mm also had higher (7%) average values for the mean platelet volume than did persons with less pocketing (Table 3). Subjects with a high percent sites with PD ≥4 mm had a slightly lower (1%) mean corpuscular volume than did subjects with fewer deep pockets. Small and barely

Table 3 Results of multiple linear regression analyses of the influence of three periodontal exposures of interest (case status, high % sites with PD ≥4 mm, or high % sites with bleeding on probing) on the natural logarithm of the hemogram parameters

	Case status	Exposures of interest % sites with PD ≥4 mm b [95% CI]	% sites with BOP b [95% CI]
EOS (10^3/μL)	–	0.73 [0.55; 0.97] p=0.03	0.76 [0.57; 1.00] p=0.05
MCV (fL)	–	0.99 [0.97; 1.00[p=0.03	–
MCH (pg/cell)	–	0.99 [0.97; 1.00] p=0.05	–
MPV (fL)	1.05]1.00; 1.10] p=0.03	1.07 [1.02; 1.12] p=0.003	–

The results presented are the back-transformed regression coefficients, which therefore have a multiplicative interpretation. The table only presents those regression models with statistically significant associations at $p \leq 0.05$. All models adjusted for age (continuous), gender, and daily smoking (yes/no)

EOS eosinophils, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MPV* mean platelet volume, *b* linear regression coefficient, *95% CI* 95% confidence interval

significant associations were found between a high percent sites with probing depth ≥4 mm and lower mean corpuscular hemoglobin.

Discussion

A total blood analysis or hemogram is frequently used to assess the presence of infection or inflammation, and the question whether periodontal infections affect hematological parameters such as the differential counts of white blood cells, red blood cells, and/or platelets has interested several research groups [1–5, 7, 13–17]. Some of these studies have documented differences in the hematological parameters for subjects with chronic periodontitis compared to healthy subjects, although the findings are not always conclusive [2, 5, 7, 15–18]. The variation found in the blood parameters investigated in adult study populations frequently appears to be modest and the values do often not exceed the normal reference values [6]. However, one of the problems in studying hematological values among adult periodontitis patients is that these are likely to reflect a host of influential factors over and beyond the periodontitis as such. One of the key reasons for undertaking the present study was that adolescents with periodontitis might constitute a much more homogeneous population with less influence of other (hidden) infectious or inflammatory factors. Thus, if the hemogram in adolescents with periodontitis is different from "normal", it would be more convincingly related to periodontal status, rather than a coincidental finding.

Despite their statistical significance, one may clearly question if hemogram differences between groups in the order of magnitude of 1–5% make any sense in clinical/biological terms. As the differences are small, it is tempting to describe them as spurious statistical results. However, the 24–27% reductions in eosinophils among subjects with a high percent sites with PD ≥4 mm or a high percent sites with BOP cannot be considered trivial differences, even though one of these was barely statistically significant owing to the variability of the eosinophil parameter.

The significant association between lower eosinophil counts and signs of periodontitis found in this study has not been reported before. However, while eosinophils are primarily recognized as terminal effectors of allergic responses and of parasite elimination [19, 20], a distinct aspect of the body's response to infection or inflammation is also a reduction in the number of circulating eosinophils [21–24]. The mechanisms underlying this reduction remain to be elucidated; however, this may be partially explained by the release of small but consistent amounts of chemotactic factors into the circulation and eosinophil accumulation at tissue sites, e.g., lymph nodes [21, 25]. Recent evidence indicates also that eosinophils play a role as antigen-presenting cells that modulate immune responses by amplifying T-helper cell type 2 (Th2) responses [19, 20, 26], and that they can selectively recognize gram-negative bacteria and become activated to release cytotoxic granule proteins that may perpetuate inflammation [25]. Taking this information together with current evidence suggesting that chronic periodontitis in humans is associated with a local Th2 response [27], we would have expected to find increased eosinophil's activity in cases of periodontitis [20]. It is unclear, however, whether functional changes of eosinophils are related to the differential cell counts according to periodontal parameters like these found in this study; and while this remains to be elucidated, our findings are in line with recent reports on the existence of an inverse association between periodontitis and Th2-mediated immune responses like respiratory allergies [28–31].

The positive association between mean platelet volume (MPV) and parameters of periodontitis found in this study has not been previously reported. At first glance, one may wonder why statistically significant differences were found for MPV in this study but not also for the platelet counts. A plausible explanation might be found in the fact that MPV correlates more closely to platelet function than do platelet counts per se [32, 33]. Higher MPV values usually reflect augmented production of young platelets and increased number of large hyper-aggregable platelets [34, 35], and for this reason MPV has been considered a suitable indicator of platelet activation [34–36]. Activated platelets release antibacterial peptides [37], but some evidence also indicates that certain pathogens may have developed a way to exploit activated platelets by binding to their surfaces to establish or propagate infection [38]. This is in agreement with the results of several studies reporting that periodontitis and periodontal pathogens may be associated with platelet activation and with a prothrombotic state [14, 33, 39–43]. An alternative explanation for the higher MPV levels among cases in our study can be found in the reported association between changes in the levels of MPV and various non-infectious inflammatory processes [44–47], which may suggest that MPV changes reflect disease activity in inflammation [45, 46]. Taking into account the relatively small (5–7%) increase in MPV levels among the cases and among subjects with more pockets ≥ 4 mm, the possibility of this been a spurious positive finding should be kept in mind.

Our findings that neither the white blood cells, the neutrophils, nor the lymphocyte values differed between groups corroborate the findings reported for Nigerian adolescents with periodontitis [7] and suggest that the inflammatory load of periodontitis in this young adolescent population is insufficient to influence these counts. The findings of two previous studies conducted among adults suggest lower number of erythrocytes, lower hematocrit values, and lower hemoglobin levels among subjects with periodontitis [3, 48], but these findings could not be confirmed in this study of adolescents.

The results of this study suggest that eosinophil counts and mean platelet volumes can be associated to parameters of periodontitis in adolescents. Despite the lack of association with traditional parameters, the study indicates also in this population a systemic effect of periodontal parameters.

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Appendix

Table 4 Range of values for hemogram for cases and controls according to gender

	Boys		Ref	Girls		Ref
	Cases	Controls		Cases	Controls	
WBC	4.70–11.80	4.02–17.60	5.0–10.0	4.24–15.4	5.03–11.50	5.0–10.0
NEU	1.91–9.34	2.09–12.80	2.8–7.0	1.35–10.0	2.26–7.63	2.8–7.0
EOS	0.02–4.68	0.01–0.97	0.0–0.4	0.01–0.85	0.47–0.70	0.1–0.4
BASO	0.03–0.15	0.02–0.16	0.0–0.2	0.02–0.14	0.04–0.14	0.0–0.2
LYM	1.21–3.92	1.05–3.31	0.9–4.5	1.16–5.01	1.64–3.95	0.9–4.5
MONO	0.35–0.79	0.31–0.99	0.1–0.2	0.28–0.94	0.30–0.84	0.1–0.2
RBC	4.59–5.87	4.4–6.09	4.5–5.0	3.72–5.36	3.91–5.05	4.0–4.5
HTC	40.8–48.8	36.9–53.6	42.0–52.0	33.8–45.7	34.2–46.1	37.0–48.0
HGB	13.6–16.6	12.3–18.3	13.0–18.0	11.4–15.5	11.8–15.7	12.0–16.0
MCV	74.0–94.0	78.3–95.0	82.0–92.0	72.7–95.7	81.0–95.0	82.0–92.0
MCH	24.6–32.4	26.5–32.8	27.0–32.0	24.2–33.1	27.4–33.6	27.0–32.0
MCHC	32.6–35.4	33.4–36.9	33.0–36.0	33.2–35.8	33.5–35.4	33.0–36.0
RDW	12.6–16.7	12.9–16.3	11.5–14.5	12.0–17.7	12.3–15.9	11.5–14.5
PLT	146–392	145–363	150–400	135–429	185–448	150–400
MPV	6.82–11.6	6.77–18.8	0.0–99.9	6.49–12.0	6.12–11.0	0.0–99.9

Reference values from the Health Reference Center Cordillera Oriente, Santiago, Chile for Abbott Cell-Dyn 3,500 automated hematology analyzer.

WBC leukocyte count, *NEU* neutrophils, *EOS* eosinophils (10^3/μL), *BASO* basophils (10^3/μL) ($\times 10^{-2}$), *LYM* lymphocytes, *MONO* monocytes (10^3/μL), *RBC* red blood cells (10^6/μL), *HTC* hematocrit (%), *HGB* hemoglobin (g/dL), *MCV* mean corpuscular volume (fL), *MCH* mean corpuscular hemoglobin (pg/cell), *MCHC* mean corpuscular hemoglobin concentration (g/dL), *RDW* red-cell distribution width (%), *PLT* platelets (10^3/μL), *MPV* mean platelet volume (fL)

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