

# Systemic Inflammation Markers in Patients With Aggressive Periodontitis: A Pilot Study

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**Background:** The association between periodontitis and systemic health is evident; however, until recently, there was a lack of scientific evidence to define the relationship between aggressive periodontitis (AgP) and systemic conditions. The aim of this study was to explore the characteristics of peripheral blood cellular and serum protein parameters in patients with AgP.

**Methods:** Patients with AgP (n = 150) and healthy controls (n = 94) were recruited. Clinical parameters, including probing depth (PD), clinical attachment level (CAL), and percentage of severe sites, were examined. Blood cell variables, including leukocyte, neutrophil, and lymphocyte counts, as well as serum protein parameters, including total protein, albumin, globulin, and albumin/globulin ratio, were analyzed.

**Results:** Elevated neutrophil numbers and serum globulin levels were observed in patients with AgP compared to controls ( $4.22 \pm 1.81 \times 10^9/l$  versus  $3.20 \pm 0.91 \times 10^9/l$  and  $29.20 \pm 3.75$  g/l versus  $27.17 \pm 3.32$  g/l, respectively;  $P < 0.01$ ). Albumin level and albumin/globulin ratio were lower in the AgP group than in the control group ( $47.65 \pm 2.45$  g/l versus  $48.88 \pm 2.13$  g/l and  $1.66 \pm 0.24$  versus  $1.83 \pm 0.24$ , respectively;  $P < 0.01$ ). In the AgP group, neutrophil counts and serum globulin levels were positively correlated with clinical parameters, including mean values for PD, CAL, and percentage of severe sites ( $P < 0.05$ ); the albumin level and albumin/globulin ratio were inversely correlated with the clinical parameters as described above ( $P < 0.05$ ).

**Conclusions:** Patients with AgP may have elevated peripheral leukocyte numbers and serum globulin levels as well as decreased serum albumin levels and albumin/globulin ratios compared to controls. These changes might be associated with the severity of periodontal destruction. *J Periodontol* 2008;79:2340-2346.

## KEY WORDS

Aggressive periodontitis; pilot studies; polymorphonuclear leukocytes.

Periodontitis is an infectious disease and is manifested as local inflammation of the periodontium. Several studies<sup>1-3</sup> have shown the systemic effect of periodontal diseases. Traditionally, an elevation in the number of peripheral leukocytes and a variation in the levels of serum proteins identified as acute-phase proteins are characteristic of infectious conditions. Changes in blood components may also be detected in patients with periodontitis. Loos et al.<sup>4</sup> reported that the number of peripheral blood leukocytes was elevated in periodontitis patients. Wakai et al.<sup>5</sup> indicated an independent association between white blood cell (WBC) count and periodontal disease severity as defined by the Community Periodontal Index of Treatment Needs (CPITN). Among patients with periodontitis, Ebersole et al.<sup>6</sup> observed relatively high levels of C-reactive protein (CRP) compared to controls. The results of Loos et al.<sup>4</sup> suggested a dose-dependent response of CRP to periodontitis.

The relationship between periodontal disease and systemic health has been well recognized through epidemiologic studies during the last decade. For example, patients with periodontal disease have a high incidence of cardiovascular diseases that are exemplified by increases in peripheral WBC count and CRP levels.<sup>7-9</sup> Modulation of cellular and protein components may be the link between periodontitis and systemic conditions. However,

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there is still a gap in knowledge regarding the relationship between systemic inflammation markers and periodontal clinical parameters. Previous reports mostly concentrated on elderly populations with chronic periodontitis. Aggressive periodontitis (AgP) is a special class of periodontal disease characterized by its early age of onset and rapid progression. There is little information on the relationship between AgP and systemic conditions.

Christan et al.<sup>10</sup> reported a decrease in peripheral leukocyte numbers after non-surgical periodontal therapy in patients with generalized AgP. Elevated leukocyte numbers in the peripheral bloodstream can be presumed in untreated patients with AgP compared to subjects with healthy periodontium. The primary aim of this study was to explore the characteristics of peripheral blood cells in patients with AgP and investigate the relationship between leukocyte numbers and the extent of periodontal destruction. Serum protein levels were also assessed in this study, because of their changes under systemic inflammatory conditions. In the present study, we focused on the total protein as well as the two major fractions, namely albumin (ALB) and globulin (GLB), because serum protein composition is diverse and complex. We also analyzed the correlations between serum protein variables and the specific serum immunoglobulin G (IgG) titers to *Aggregatibacter actinomycetemcomitans* (*Aa*; previously *Actinobacillus actinomycetemcomitans*), including serotypes a, b, and c in patients with AgP because *Aa* has been identified as one of the pathogenic bacteria for AgP.<sup>11,12</sup>

## MATERIALS AND METHODS

### Study Population

One hundred fifty-two patients with generalized AgP (62 males and 90 females), aged 14 to 42 years, were recruited from the Clinic of the Periodontology Department, Peking University School and Hospital of Stomatology, from July 2001 to May 2006. The diagnosis criteria were defined according to the classification developed at the International Workshop for a Classification of Periodontal Diseases and Conditions in 1999:<sup>13</sup> the onset of periodontal disease generally occurred at <35 years of age, and there were at least eight teeth with probing depth (PD) >6 mm and with radiographic evidence of alveolar bone loss. At least three of these teeth were not first molars or incisors. Other factors were also considered: family aggregation, rapid progression, and the relationship between local factors and periodontal destruction.

Ninety-four healthy control subjects (33 males and 61 females), aged 20 to 48 years, were selected from the staff and students of the Peking University School and Hospital of Stomatology. The inclusion criteria were no site with clinical attachment loss, no site with

PD >3 mm, no bone loss on radiographs, and the percentage of sites with bleeding on probing (BOP) was <10%.

The exclusion criteria were systemic diseases, smoking, periodontal therapy within the previous year, antibiotics within the previous 3 months, and pregnancy.

By their own acknowledgment, all study subjects were free of systemic disease and were not taking any medication known to affect periodontal status. All recruited subjects accepted a comprehensive blood examination and were referred to physicians when necessary. Two patients with AgP were diagnosed as having type 2 diabetes and were excluded. Consequently, 150 patients with AgP participated in the present study.

All subjects belonged to the Han race, which makes up the majority of the Chinese population. Each study subject filled out a questionnaire that noted general background (including weight and height), medical and dental care history, oral hygiene habits, and social status. The body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. The present study was conducted with the written informed consent of all subjects and was approved by the Ethics Committee of the Peking University Health Science Center.

### Clinical Assessment

Full-mouth periodontal examinations were conducted using a Williams periodontal probe. PD and clinical attachment level (CAL) were measured at six sites (mesial, distal, and middle sites of the buccal and lingual sides) per tooth. CAL was measured as the distance from the bottom of the pocket to the cemento-enamel junction. The highest bleeding index (BI)<sup>14</sup> values of the buccal and lingual surfaces were recorded. The percentage of surfaces with BOP was calculated. The third molars were excluded from the examination.

A site with PD >6 mm and CAL >5 mm was defined as a severe site. The percentage of severe sites was calculated. Clinical examinations were done by two skilled, calibrated practitioners. Calibration was performed on 10 patients with severe periodontitis before the present study began. Of the replicated measurements for each examiner, 98.0% and 96.8% were within 1 mm for PD, and 94.9% and 92.4% were within 1 mm for CAL. Of the paired measurements between the two examiners, 93.5% were within 1 mm for PD, and 89.8% were within 1 mm for CAL.

### Blood Examination

A peripheral blood sample was obtained from each fasting examinee by venipuncture between 8:00 and 10:00 am and was divided into two tubes. One tube contained EDTA and was used for blood cell analysis

by hematology analyzers;† the other did not contain EDTA and was used for serum protein analyses by biochemical analyzer.‡ Blood cell analysis included WBC count, neutrophil count, lymphocyte count, neutrophil percentage, lymphocyte percentage, platelet count (PLT), and mean platelet volume (MPV). Serum protein parameters included total protein (TP), ALB, GLB, and albumin/globulin ratio (A/G). The specific serum IgG titers to Aa were measured by enzyme-linked immunosorbent assay.

### Statistical Analysis

The differences in clinical variables between the diseased and healthy groups were analyzed by the Student *t* test. The blood cell and protein variables were analyzed with the analysis of covariance model, controlling for age, gender, and BMI as confounders. Partial correlation coefficients between the clinical and hematologic parameters in the AgP group were determined, controlling for the potential confounders mentioned above. Partial correlation analyses were also conducted between serum protein variables and specific serum IgG titers to Aa. For all analyses, only *P* values <0.05 were considered statistically significant.

## RESULTS

The population variables are shown in Table 1. The mean ages of AgP and control groups were 27.3 ± 5.8 and 26.8 ± 5.2 years, respectively. There was no difference in the mean values for age and BMI between the two groups, and no significant difference for gender distribution.

The clinical variables for the two groups are presented in Table 1. For the AgP group, the mean values for PD and CAL were 4.8 ± 2.1 mm and 4.7 ± 2.8 mm, respectively; the mean BI and BOP were 3.7% ± 0.6% and 99.4% ± 3.0%, respectively, and the mean number of teeth was 26.4 ± 3.5. There were significant differences for all clinical variables between the AgP group and the control group (*P*<0.01).

The results of the blood cell analysis are shown in Table 2. Compared to controls, significantly higher total WBC count, neutrophil percentage, and neutrophil count were observed in the AgP group (Figs. 1 through 3). Lymphocyte count and percentage were significantly lower in the AgP group than in the control group (*P*<0.01).

The serum protein variables are presented in Table 3. The patients with AgP had significantly lower mean values for ALB and A/G than the control group (*P*<0.01; Figs. 4 and 5). The mean GLB level was significantly higher in the AgP group than in controls (*P*<0.01; Fig. 6). The serum IgG titers to Aa serotypes a, b, and c were positively correlated with GLB level (*R* = 0.24, 0.25, and 0.29, respectively; *P*<0.05) and negatively correlated with A/G (*R* = 0.23, 0.27, and 0.31, respectively; *P*<0.05) (data not shown).

**Table 1.**

### Clinical Parameters (mean ± SD) of Control and AgP Groups

	Control Group (n = 94)	AgP Group (n = 150)
Gender (male/female)	33/61	61/89
Age (years)	26.8 ± 5.2	27.3 ± 5.8
BMI (kg/m <sup>2</sup> )	21.5 ± 2.7	22.1 ± 3.8
PD (mm)	2.3 ± 0.7	4.8 ± 2.1*
CAL (mm)	0 ± 0	4.7 ± 2.8*
BI	0.7 ± 0.7	3.7 ± 0.6*
BOP (%)	5.8 ± 2.9	99.4 ± 3.0*
Severe sites (%)	0 ± 0	36.0 ± 20.0*
Teeth (n)	28.0 ± 0	26.4 ± 3.5*

\* Compared to control group (*P*<0.01).

**Table 2.**

### Values (mean ± SD) of Blood Cell Variables in Control and AgP Groups

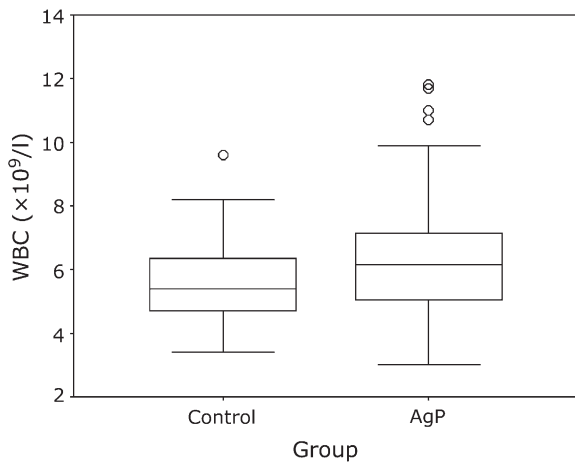
	Control Group (n = 94)	AgP Group (n = 150)
WBC (×10 <sup>9</sup> /l)	5.64 ± 1.28	6.37 ± 2.02*
Neutrophils (%)	56.40 ± 7.77	64.61 ± 8.92*
Lymphocytes (%)	36.25 ± 7.43	29.57 ± 8.41*
Neutrophils (×10 <sup>9</sup> /l)	3.20 ± 0.91	4.22 ± 1.81*
Lymphocytes (×10 <sup>9</sup> /l)	2.03 ± 0.59	1.79 ± 0.48*
PLT (×10 <sup>9</sup> /l)	226.93 ± 50.90	214.60 ± 51.72
MPV (fl)	9.27 ± 0.93	9.01 ± 0.86

\* Compared to the control group (*P*<0.01).

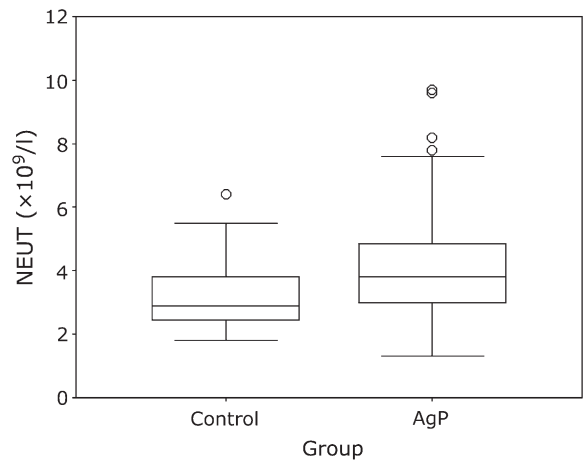
The results of partial correlation analyses between blood variables and clinical parameters in patients with AgP are shown in Table 4. The leukocyte and neutrophil counts were positively correlated with mean values for PD, CAL, and percentage of severe sites. ALB and A/G were negatively correlated with the clinical parameters mentioned above. A positive correlation was observed between GLB level and the clinical parameters; the correlation coefficients ranged from 0.21 to 0.35.

† SYSMEX KX-21, Sysmex, Kobe, Japan.

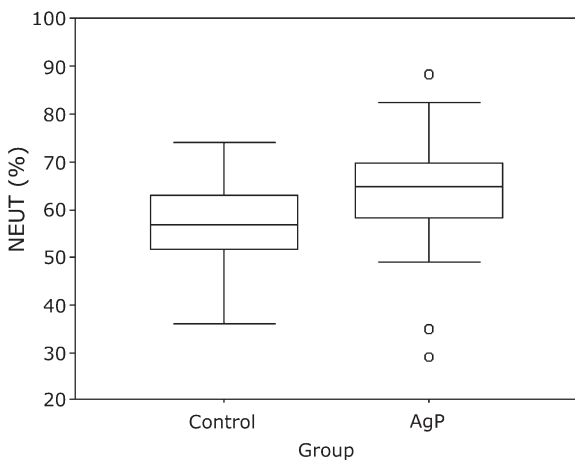
‡ HITACHI 7060, Hitachi, Tokyo, Japan.



**Figure 1.** WBC counts of control and AgP groups ( $5.64 \pm 1.28 \times 10^9/l$  versus  $6.37 \pm 2.02 \times 10^9/l$ ;  $P < 0.01$ ). o = extreme outliers.



**Figure 3.** Neutrophil (NEUT) counts of control and AgP groups ( $3.20 \pm 0.91 \times 10^9/l$  versus  $4.22 \pm 1.81 \times 10^9/l$ ;  $P < 0.01$ ). o = extreme outliers.



**Figure 2.** Neutrophil (NEUT) percentages of control and AgP groups ( $56.40\% \pm 7.77\%$  versus  $64.61\% \pm 8.92\%$ ;  $P < 0.01$ ). o = extreme outliers.

**DISCUSSION**

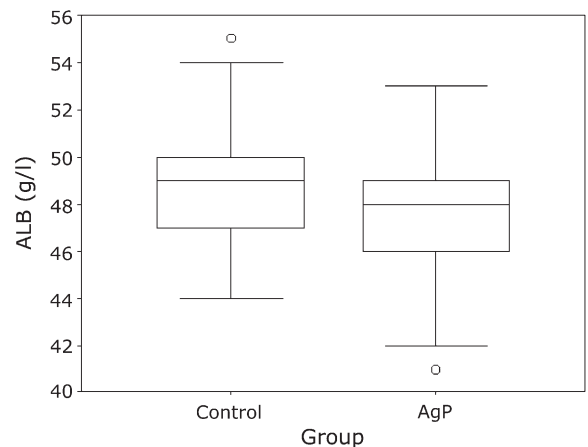
The elevation of WBC counts in peripheral blood has been used as a traditional method to diagnose an infection or inflammatory disease. Kweider et al.<sup>15</sup> first reported higher numbers of peripheral leukocytes in periodontitis patients compared to healthy controls in 1993. Several other researchers<sup>10,16,17</sup> subsequently reported similar results. A study<sup>10</sup> indicated a decrease in the numbers of leukocytes after non-surgical periodontal therapy in 27 patients with generalized AgP. Previous studies suggested that there might be a dose-response relationship between peripheral numbers of WBCs and periodontitis. Loos et al.<sup>4</sup> investigated the blood cell components in patients with localized and generalized periodontitis; they

**Table 3.**

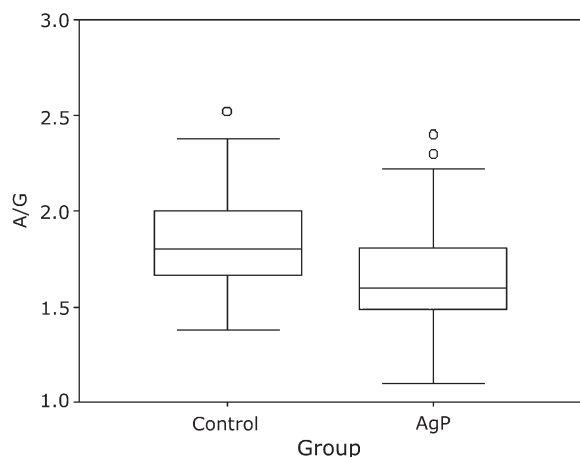
**Values (mean  $\pm$  SD) of Serum Protein Variables in Control and AgP Groups**

	Control Group (n = 94)	AgP Group (n = 150)
TP (g/l)	76.05 $\pm$ 3.89	76.85 $\pm$ 4.38
ALB (g/l)	48.88 $\pm$ 2.13	47.65 $\pm$ 2.45*
GLB (g/l)	27.17 $\pm$ 3.32	29.20 $\pm$ 3.75*
A/G	1.83 $\pm$ 0.24	1.66 $\pm$ 0.24*

\* Compared to control group ( $P < 0.01$ ).

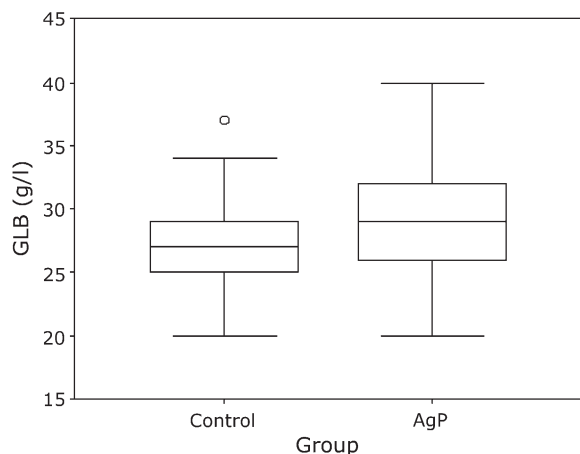


**Figure 4.** Serum ALB levels of control and AgP groups ( $48.88 \pm 2.13$  g/l versus  $47.65 \pm 2.45$  g/l;  $P < 0.01$ ). o = extreme outliers.



**Figure 5.**

Serum A/G levels of control and AgP groups ( $1.83 \pm 0.24$  versus  $1.66 \pm 0.24$ ;  $P < 0.01$ ). o = extreme outliers.



**Figure 6.**

Serum GLB levels of control and AgP groups ( $27.17 \pm 3.32$  g/l versus  $29.20 \pm 3.75$  g/l;  $P < 0.01$ ). o = extreme outliers.

found that the numbers of peripheral WBCs increased with the increasing severity and extent of periodontitis. Wakai et al.<sup>5</sup> reported an independent association between WBC count and periodontal disease severity defined by CPITN. In accordance with the previous reports, the present study showed that patients with AgP had higher numbers of peripheral WBCs than controls. As expected, the numbers and percentages of neutrophils in patients with AgP were much higher than in healthy controls ( $4.22 \pm 1.81 \times 10^9/l$  versus  $3.20 \pm 0.91 \times 10^9/l$  and  $64.61\% \pm 8.92\%$  versus  $56.40\% \pm 7.77\%$ , respectively;  $P < 0.01$ ), although the values were inside the reference range. Meanwhile, the total numbers of leukocytes and neutrophils were positively associated with the severity and extent of periodontitis described by mean PD, CAL, and percentage of severe

**Table 4.**

**Partial Correlation Coefficients Between Blood Variables and Clinical Parameters in Patients With AgP, Controlling for Age, Gender, and BMI as Potential Confounders**

	Mean PD	Mean CAL	Severe Sites Percentage
WBC	0.26*	0.32*	0.21†
Neutrophil count	0.26*	0.32*	0.21†
TP	0.16	0.09	0.12
ALB	-0.20†	-0.24*	-0.22*
GLB	0.30*	0.26*	0.28*
A/G	-0.35*	-0.32*	-0.33*

\*  $P < 0.01$ .

†  $P < 0.05$ .

sites. The increasing tendency of the number of systemic neutrophils is the same as the neutrophils infiltrated in local inflammatory periodontal tissues. Previous studies<sup>18-20</sup> demonstrated that the leukocytes' infiltration into periodontal tissues corresponded with the periodontal status. The inflammatory cytokines released from periodontal infection sites may be a connection between the local and systemic response to periodontal pathogens.

The neutrophil cell is a major cellular component of the human innate defense system, particularly against bacterial infection. Studies of the host response in periodontal diseases considered neutrophils as the key protective cell, and defective neutrophil function is associated with periodontal destruction. Deficient neutrophil function often results in an increased susceptibility to periodontitis. A number of studies<sup>21-23</sup> reported on neutrophil abnormalities in aggressive periodontitis, including abnormalities in adherence, chemotaxis, superoxide generation, phagocytosis, and bactericidal activity.

Changes in the cellular components, even within the normal range, of peripheral blood are associated with systemic conditions of the host. The elevation of blood leukocyte count may be a risk factor for coronary heart disease,<sup>7-9</sup> and MPV may be an independent risk factor for stroke and coronary atherosclerosis.<sup>24,25</sup> Changes in blood cell variables may be a way that periodontitis affects systemic health.

The present study showed that the ALB level and A/G were significantly lower, whereas the GLB level was elevated in patients with AgP compared to controls. Previous studies demonstrated changes in the plasma proteins profile during acute inflammation. Plasma ALB was proved to be lower during experimental

inflammation.<sup>26</sup> A recent study<sup>27</sup> indicated the association between the numbers of root caries and lower serum ALB levels. The serum CRP and immunoglobulin levels were elevated in patients with periodontitis.<sup>4,6,28,29</sup> CRP and immunoglobulin are both within the  $\gamma$ -globulin fraction by protein electrophoresis. Ranney et al.<sup>30</sup> observed higher serum IgG in young adults with severe periodontitis than in healthy controls. Our data indicated that the serum IgG titers to Aa might be positively correlated with GLB levels and inversely associated with A/G in patients with AgP. These results suggested that changes in the serum protein profiles might be associated, at least in part, with the elevation in serum antibody levels to specific periodontal pathogens. The elevation of serum levels of CRP and antibodies to periodontal pathogens were recently proved to be risk factors for coronary heart disease and stroke.<sup>8,31,32</sup> The decrease in A/G may result from the decrease in ALB level as well as the elevation in the GLB level. A/G correlated positively with the clinical parameters in patients with AgP, and it might be a sensitive systemic index that reflects the severity and extent of AgP. However, the differences in cellular and protein variables between the two groups in this study were minor, although some of them were statistically significant. The correlation coefficients were relatively low (<0.4). Other factors that may affect the blood cell numbers and protein levels, such as nutrition status, subclinical diseases, and living habits, were not considered. More studies are needed to demonstrate the systemic effect of periodontal infection.

## CONCLUSIONS

This study focused on a young and middle-aged population with AgP. Patients with AgP had elevated peripheral leukocyte numbers and serum GLB levels as well as decreased serum ALB levels and A/G compared to healthy controls. AgP may have some effect on systemic inflammation markers, and the systemic effect of AgP might be associated with the severity and extent of periodontal destruction.

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