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The Markers of Systemic Inflammation in Patients with Chronic Periodontitis: Leukocytes, C-reactive Protein and Fibrinogen

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Abstract ***Background:*** Periodontitis has been identified as potential risk factors for systemic pathologies. The aim of this study was to investigate the relationship between periodontitis and systemic inflammatory markers, as well as, if there is a relation to severity of periodontitis. ***Methodology:*** Periodontal examinations and serum markers of inflammation levels mesaurements were performed in 50 patients. The patients with moderate periodontitis had low CAL and PD < 5mm. The patients with severe periodontitis were with high CAL and PD > 5mm. The clinical parameters of periodontitis were determined among all subjects. The LEU, CRP, and FIB for the present investigation were obtained from peripheral venous blood patients from all groups. ***Findings:*** In both moderate and severe periodontitis, the results indicated that the total leukocytes count and neutrophils had a significantly higher count ($p < 0.001$) among the groups with periodontitis but that there was no significance in the lymphocytes counts. The results also show a significant relation between indicators of poor periodontal status and increased levels CRP and fibrinogen. ***Conclusion:*** Periodontitis is associated with an enhanced inflammatory response expressed by higher levels of inflammatory markers. The extent of increase in these marker levels in periodontitis patients depends of severity of the disease. ***Significance:*** The association of periodontitis with WBC, CRP and fibrinogen levels appears to be contributing factors for CVD and might be a possible intermediate pathway in this association.

Keywords: *leukocyte, neutrophil, inflammation, periodontitis,C-reactive protein, fibrinogen*

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1. Introduction

The concept that inflammation play important part in pathophysiology of atherosclerosis and its complication, coronary artery disease, has provided a new unifying hypothesis of the links between risk factors and the cellular and molecular alterations that underlie this disease [1]. This new mechanistic insight has already begun to translate into changes in clinical practice. The preponderance of available data supports the predictive power of biomarkers of inflammation such as white blood cells (WBC), C-reactive protein (CRP) and fibrinogen in broad categories of individuals, both those as apparently well and those with alredy-manifest atherosclerotic cardiovascular disease. The demonstrated clinical utility of CRP and potentially of other inflammatory biomarkers (WBC, fibrinogen) has engendered intense interest in evaluating their effectiveness as predictive conventional risk markers and as goals for therapy. The insight that inflammation play a fundamental role in atherosclerosis process in the pathophysiology of coronary artery disease may lead to novel therapies that target aspects of the inflammatory process smoldering within the atheroma [2].

In recent years, great attention of the world researchers has been focused on a possible association between oral health and systemic diseases, so that numerous contradictory results can be found in the literature [3,4,5,6]. The presence of infection in an organism can bring an increased risk of systemic diseases as a result of bacteria and bacterial products, such as endotoxin (lipopolysacharide) or the effects of synthesized mediators [7,8]. These infections are usually well-known, but also can be the "infections of unknown etiology". Periodontitis has recently been identified as a potential risk factor for systemic pathologies such as cardiovascular disease [9]. The hypothesis being that local periodontitis triggered by bacterial insult, is chronic inflammmatory disease and that production of circulating cytokines may contribute to the development of atherosclerosis, cardiovascular disease, premature birth of children with small body weight and diabetes [10-15]. Although periodontitis is chronic in nature, acute-phase elements are also part of the innate immunity in periodontitis and confirm that in periodontitis a systemic inflammation is present [16]. The importance

of the association between periodontal disease, as a local infection, and systemic diseases requires further investigations and opens new possibilities for an old concept, that is a "focal infection" [9,17].

Most studies have examined the relation between periodontitis and markers of systemic inflammation in predominantly race/ethnicity population [18]. Whether this association exists in a Serbian populations is not well documented. We hypothesized that periodontitis may result in an enhanced systemic inflammatory response with higher levels markers of systemic inflammation (leukocytes, C-reactive protein and fibrinogen) in Serbian population in Nis.

The aim of this pilot study was to investigate and compare levels of systemic inflammation markers (the total count of leukocytes, neutrophils, CRP and fibrinogen) in the peripheral blood of patients suffering from different forms of severity of chronic periodontitis. A second aim was to evaluate whether level markers of inflammation were in a relation to severity of periodontitis in a Serbian population in Nis.

2. Material and Methods

2.1. Choice of Patients

The investigation included the total of 75 patients, fifty subjects with periodontitis (22 females and 28 males) and 25 persons without periodontitis (11 women and 14 men), chosen from the patients who visited for the first time the Department of Periodontology and Oral Medicine, of Medical Faculty in Nis. After being informed on the purpose of the study, all patients gave informed consent. The study protocol was approved by the Ethical committee of Medical Faculty in Nis, Serbia (No:01-2800-5).

Exclusion criteria was any dental treatment during the past 6 months. Patients were also free from other infections, inflammatory diseases, diabetes mellitus, malignancy, cardiovascular disease and antiinflammatory and antibiotics treatment.

The patients were examined and grouped according to their periodontal status. This classification was based on an original index of severity of periodontal disease based on several references [5,19,20]. Thus, the patients were classified into two groups: I group (n = 24 patients) are patients with moderate periodontitis with pocket depth < 5 mm and with moderate mean clinical attachment loss (2.0 mm). The second group (n = 26 patients) are those with severe periodontitis with pocket depth > 5 mm and with high mean attachment loss (3.0 mm).The third group included 25 subjects without periodontitis and gingival sulcus < 2 mm.

2.2. Periodontal Research

All the patients were examined at the beginning, when they came to the Department for the first time. Clinical research involved the measuring of the periodontal pockets depth (PPD) at six points per teeth and bleeding on probing (BOP). Bleeding on probing (BOP) was measure if bleeding occurred immediately after probing from pocket depth, and it was reported as positive. The gingival bleeding index was categorized into: 0-no bleeding, 1-bleeding 10sec after probing, 2–bleeding whitin probing and 3 – posibility of spontaneuos bleeding.

Periodontal pocket depth was measured with a standard periodontal probe (Michigen 0). Periodontal pocket depth < 5mm (moderate periodontitis) and > 5mm (severe periodontitris) were measured as the distance in millimeters from the free gingival margin to the bottom of the pocket.

Attachment loss (AL) was measured with a standard periodontal probe within as the distance in millimeters from the cemento-enamel junction to the bottom of the pocket. The value < 3 mm was for moderate periodontitis and > 3 mm for severe periodontitis.

Control group (healthy gingiva) was without bleeding on probing, gingival sulcus < 2mm, and no attachment loss.

2.3. Biochemical Analysis

The samples of peripheral vein blood for the determination of the total leukocyte and neutrophile count, CRP levels and fibrinogen, were taken according to the statndard methods in the morning hours, and were processed in the Central laboratory for biochemical researches, Clinical Center Nis. The values used for the analysis were mean values obtained for these markers. For the total leukocyte count the vaule was $6.5x10^9$/l, and for fractions in the leukocyte formula the values were the following: $4.7x10^9$/l for neutrophiles, and $2.4x10^9$/ for lymphocytes.

Serum CRP concetration was quantified in milligrams per liter using radial immunodiffusion assay. Thus, for study purposes, CRP levels were used to divide patients in low (CRP concentrations < 5 mg/l) and high levels categories (CRP concentrations > 5 mg/l), and for fibrinogen serum concentracion is 2-4g/ml according to data of Central Clinical Biochemical Laboratory of University Clinic in Nis. Demographic variables included age, sex, and the body mass index (weight-kg/height-m^2).

2.4. Statistical Analysis

Statistical analysis was performed by descriptive and analytical statistical methods by using the standard program for data processing - MS EXCEL and program package SPSS version 10.0. The following statistical parameters were analyzed: arithmetic mean (Xm), standard deviation (SD), coefficient of variation (CV), and varia tion interval (min-max).

Testing the frequency of occurence was performed by χ^2 test. Testing the mean values was conducted by variance analysis, with the following homogenous post hoc (ANOVA) test or Kruskal-Wallis test for inhomogenous data. We compared characteristics of the study groups using, and chi-square test for categorical data, and analysis of variance for continuous data. We evaluated potential confounders by using the Dunnet T3 test. Potential confounders considered in these analyses were age, gender, body mass index (BMI).

3. Results

3.1. Periodontal Clinical Parameters

In both groups of patients suffering from periodontitis there were evident changes in the values of the analyzed clinical parameters of periodontitis compared to the group of individuals with healthy periodontium. The elevated values of DPP and BOP are presented in Table 1.

Table 1. Mean values of clinical parameters (periodontal pockets depths and bleeding on probing) in all examinees

Periodontal pockets depths - PPD							
Group	**Nº**	**Xm**	**SD**	**CV**	**Min**	**Max**	**ANOVA**
I Moderate PD	24	3.91	0.36	9.29	3.1	4.3	F = 221.03 p = 0.000 ***p<0.001***
II Severe PD	26	5.65	0.57	10.04	5.1	7.0	
III Healthy	25	2.41	0.28	11.73	2.0	2.8	
Total	75	3.99	1.39	35.05	2.0	7.0	
Bleeding on probing - BOP							
Group	**Nº**	**Xm**	**SD**	**CV**	**Min**	**Max**	**Kruskal Wallis Test**
I Moderate PD	24	1.13	0.35	31.06	0.50	1.70	Chi-Square = 20.708 p = 0.000 ***p<0.001***
II Severe PD	26	1.61	0.51	31.51	1.00	2.50	
III Healthy	25	0.19	0.11	54.85	0.10	0.40	
Total	75	1.15	0.66	57.95	0.10	2.50	

Footnotes: **PPD** – periodontal pocket depth; **PD** – periodontitis; **Nº** – number of examiners; **Xm** – arithmetic mean; **BOP** – bleeding on probing; **SD** – standard deviation; **CV** – coefficient of variation; **Min** – minimum; **Max** – maximum

In both groups of patients with periodontitis, the values of clinical parameters of periodontitis were elevated compared to the group of individuals with healthy gums.

There was a difference in these values between the groups of patients with periodontitis. In the severe form of periodontitis the values of clinical parameters were considerably higher in comparison to its moderate form.

The patients with severe form periodontitis, when compared to the patients with moderate form of periodontitis, had deeper periodontal pockets (II-5.65; I-3.91) (Tab.1), more bleeding on probing (II-1.61; I-1.13) (Tab.1). These values are in conformity with the clinical definition of both forms of periodontitis. The values obtained for the group of examinees with healthy parodont confirmed a relatively healthy paradontium (PPD-2.41; BOP-0.19).

3.2. Results of Biochemical Analysis

In both groups of patients with periodontitis, with evident clinical symptoms of periodontitis which were determined by clinical parameters, the elevated total leukocyte and neutrophil counts were obtained (II-8.95x10^9/l; I-7.60 x10^9/l; i II-6.96x10^9/l; I-5.29x10na 9/1) compared to the group of healthy examinees (I-6.70x10^9/l; I-2.27x10^9/l).

Table 2. Mean values of biochemical parameteres (leukocytes, neutrophils, lymphocytes) in all patients

Leukocytes							
Group	Nº	Xm	SD	CV	Min	Max	**Kruskal Wallis Test**
I Moderate PD	24	7.60	2.44	32.10	4.80	14.20	Chi-Square = 3.469 p = 0.176 ***p>0.05***
II Severe PD	26	8.95	3.41	38.08	4.41	14.30	
III Healthy	25	6.70	1.44	21.53	4.00	9.00	
Total	75	7.75	2.67	34.44	4.00	14.30	
Neutrophils							
Group	Nº	Xm	SD	CV	Min	Max	**Kruskal Wallis Test**
I Moderate PD	24	5.29	2.36	44.57	2.82	11.60	Chi-Square = 29.057 p = 0.000 ***p<0.001***
II Severe PD	26	6.96	2.87	41.25	3.33	12.80	
III Healthy	25	2.27	0.83	36.78	0.57	3.56	
Total	75	4.84	2.91	60.14	0.57	12.80	
Lymphocytes							
Group	Nº	Xm	SD	CV	Min	Max	**Kruskal Wallis Test**
I Moderate PD	24	2.78	0.40	19.09	1.50	2.80	Chi-Square = 0.294 p = 0.863 ***p>0.05***
II Severe PD	26	2.94	2.52	85.43	0.60	9.50	
III Healthy	25	1.95	0.77	39.68	0.35	2.90	
Total	75	2.32	1.56	67.37	0.35	9.50	

Footnotes: **PD** – periodontitis; **Nº** – number of examiners; **Xm** – arithmetic mean; **SD** – standard deviation; **CV** – coefficient of variation; **Min** – minimum; **Max** – maximum

Mean value of the total leukocyte count was higher in second group of patients suffering from severe form of periodontitis compared to the first group with moderate form of periodontitis; however, the difference was not statistically different. In both groups the values were higher when compared to the group of healthy examinees (6.7x10^9/l), in which the mean values were close to the one used for comparison (6. 5x10^9/l).

Mean value of neutrophils, in the leukocyte formula, in the patients with severe form of periodontitis, was statistically increase (6.96x10^9/l) compared to the moderate form with the value of 5.29x10^9/l. Both values

were higher when compared to the values of healthy persons (III-2.27x10^9/l) and the mean value given by the Central laboratory for biochemical researches of the Clinical Center Nis(2.4x10^9/l), which served for comparison.

In respect to the lymphocyte count, the results showed that there was not an evident difference among the groups with periodontitis (II-2.94x10^9/l; I-2.78x10^9/l) compared to the group of healthy subjects (III-1.95x10^9/l).

It was obvious that there was a positive correlation between the clinical parameters of periodontitis showing the severity of disease and the total leukocyte and neutrophil counts in the peripheral blood.

Table 3. Characteristics of study participants by periodontal status

	PERIODONTITIS - PD				TEST
	Moderate PD	**Severe PD**	**Control group**	**Total**	**Pearson Chi –Square**
Total, N°, %	24 (32%)	26 (34.7%)	25 (33.3%)	75 (100%)	
Gender, N°, %					
male	12 (16.0%)	11 (14.7%)	7 (9.3%)	30 (40.0%)	χ^2 = 2.558 p = 0.278
female	12 (16.0%)	15 (20.0%)	18 (24.0%0	45 (60.0%)	
BOP, N°, %					
0	0 (0%)	0 (0%)	6 (9.8%)	6 (9.8%)	
1	9 (14.8%)	3 (4.9%)	4 (6.6%)	16 (26.2%)	χ^2 = 38.634 p = 0.000
2	15 (24.6%)	23 (37.7%)	1 (1.6%)	39 (63.9%)	
3	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
CRP, N°, %					
<5mg/l	14 (18.7%)	12 (16.0%)	24 (32.0%)	50 (66.7%)	χ^2 = 15.353 p = 0.000
>5mg/l	10 (13.3%)	14 (18.7%)	1 (1.3%)	25 (33.3%)	
FIBR, N°, %					
<4g/l	20 (26.7%)	10 (13.3%)	23 (30.7%)	53 (70.7%)	χ^2 = 14.267 p = 0.000
>4,g/l	4 (5.3%)	16 (21.3%)	2 (2.7%)	22 (29.3%)	

Footnotes: **PD** – periodontitis; **BOP** – bleeding on probing; **CRP** – C reactive protein; **FIBR** - fibrinogen

Table 4. Clinical and biochemical profiles of the study population

	Post Hoc Test Dunnett T3	**Moderate (m) Mean ± Std**	**Severe (s) Mean ± Std**	**Control (c) Mean ± Std**	**Total Mean ± Std**	**ANOVA**
AGE	m≈s c#m c#s	47.96±17.21	49.69±16.49	26.28±3.63	41.33±17.42	F = 22.058 p = 0.000
BMI	c≈m≈s c#s	23.83±3.39	24.82±4.01	21.59±3.90	23.43±3.98	F = 4.858 p = 0.010
PPD	c # m #s	3.82±0.57	5.27±0.70	1.76± 0.39	3.64±1.57	F = 244.286 p = 0.000
CAL	c # m #s	2.05±0.53	3.78±0.83	0.25±0.19	2.75±1.29	F = 68.471 p = 0.000
CRP	m≈s m#c s#c	4.93±3.23	8.25±9.35	1.09±1.48	6.59±7.31	F = 10.168 p = 0.000
FIBR	m≈s m#c s#c	4.29±0.83	5.19±1.57	2.80±0.86	5.32±4.89	F = 14,274 p = 0.000

*Footnotes:***BMI** – body mass index; **PPD** – periodontal pocket dept; **CAL** – clinical attachment loss; **FIBR –** fibrinogen; **CRP** – C reactive protein; **m** – moderate periodontitis; **s** – severe periodontitis; **c** – control group

Patients with periodontitis were older (severe periodontitis-49.69±16.49; moderate periodontitis-47.96±17.21), had a higher body mass index (severe periodontitis-24.82±4.01; moderate periodontitis-23.83±3.39), compared with patients without periodontitis (age- 26.28±3.63; BMI - 21.59±3.90).

When analyzed as continuous variables, each indicator of periodontal health might be associated with age and body mass index.

Mean CRP levels were significantly higher (8.25 mol/l) among subjects with periodontal pocket depth >5mm, approximately one-half greater than the patients with less depth periodontal pockets, <5mm (CRP-4.93mol/l). Mean serum CRP levels were significantly higher in the patients with periodontitis when compared to healthy controls (1.09mol/l) (p = 0.000).

Mean fibrinogen levels were significantly higher (5.19g/l) among subjects with periodontal pocket depth >5mm than the patients with less depth periodontal pockets, <5mm (4.29g/l). Mean serum fibrinogen levels were significantly higher in the patients with periodontitis when compared to healthy controls (2.80g/l)(p = 0.000)

Subjects with severe periodontitis and high levels of mean clinical attachment loss (3.78mm) had significantly higher mean CRP levels (8.25±9.35mol/l) and mean fibrinogen levels (5.19g/l) than subjects with moderate periodontitis and lower levels of mean clinical attachment loss (2.05±0.53mm) (mean CRP levels 4.93±3.23mol/l and mean fibrinogen levels 4.29g/l). In the control group CRP was very low (1.09±1.48mol/l) and fibrinogen, too (2.80g/l).(p = 0.000)

The periodontal parameters (BOP and PPD) were significantly correlated with CRP and fibrinogen in periodontal patients, specially in the group patients with severe periodontitis (p = 0.001, p = 0.000).

The CRP levels and fibrinogen were adjusted for factors known to be associated with elevated CRP, including age, add body mass index (BMI). Age and BMI were found to be significant covariates (p = 0.002, p = 0.003). Multivariate linear regression showed that CRP levels and fibrinogen were increased in subjects with periodontitis and compared with the controls, adjusted for age, gender, body mass index and periodontal parameters (BOP, AL PPD).

4. Discussion

In the present study demonstrated an increase in the total counts leukocytes and neutrophiles in the patients with severe form of chronic periodontitis (II-8.95x10^9/l; II-6.96x10^9/l), compared to the subjects with moderate form of periodontitis (I-7.60x10^9/l; I-5.29x10^9/l). The findings in this research confirm the concept that stronger inflammation of the periodontium reported in the group of examinees with severe form of periodontitis can be the result of enhanced response of the total counts leukocytes and neutrophiles from the peripheral blood, which is in conformity with the basic function of leukocytes in infections and inflammations [21]. Leukocytes, before all polymorphonuclear leukocytes are the major systemic cells of phagocytosis and the first cells of the host defense mechanism against infective agents [22]. During periodontitis, as a bacterial infection, leukocytes are initially predominant cells of the host defense mechanism, and have a significant role in inflammation and pathogenesis [23,24]. The changes in the total counts leukocytes and neutrophiles in the leukocyte formula point to the presence of infection and inflammation, which can be the risk factor for systemic conditions and diseases [25].

The analyses of the data from a sample representative for the Serbian population in Nis support the existence of a signaficant relation between periodontal health status, leukocytes, serum CRP levels and serum fibrinogen levels. The association of periodontitis i CRP levels and serum fibrinogen levels appears to be independent of other contributing factors in patients with periodontitis and increased CRP levels associated significantly with risk of any stroke and risk of ishemic stroke [26] after adjusting for tradicional risk factors. In this study statistical analysis were performed with adjustment for potential confounders such as age, gender, and body mass index. These results were in accordance with results other reported [18,27,10,28].

The results of this study confirmed those of previous study conducted with subjects that showed a significant association between dental disease and CVD [29,30,31]. Dorn et al. suggest that the capacity of the oral biofilm bacteria to invade not only the periodontal tissues but also the tissues of coronary arterias makes them possible factors connecting periodontitis and coronary artery disease [32].

Kweider et al. [33] have shown that the patients suffering from periodontitis have significantly higher counts of leukocytes and fibrinogen levels when compared to the control subjects. Inflammatory oral diseases, such as periodontitis, can influence the total leukocyte and neutrophil counts in the circulation considerably. The total leukocyte and neutrophil counts, as indicators of inflammation, at the same time show the association between oral disease, especially periodontitis, and systemic diseases in which the infection is an etiological factor (in cardiovascular diseases, especially myocardial infarction) [34,35]. After the initial publication of Mattila et al, [36] that patients with periodontal infections had significant elevations of plasma fibrinogen and white blood cell count, a subsequent study observed that periodontitis was also associated with other markers of activated inflammation and hemostasis, including CRP [33]. This plasma biomarker that reflect the clinical potential of atherothrombotic disease may allow more precise prognostication in high-risk populations, and perhaps earlier diagnosis and intervention in patients at risk for or with occult cardiovascular disease [8] and to improve vascular risk prediction in primary and secundary prevention [37].

In his review paper, Bruno presents the current knowledge on the levels of certain markers of inflammation in periodontitis, among which the accompanying cellular factors of the peripheral blood: total leukocyte, erythrocyte and thrombocyte counts, as well as other plasma proteins (C-reactive protein) [38]. The majority of systemic factors of inflammation, among which the leukocytes, are predictable factors, that is the markers of systemic diseases [39,40]. The subgingival biofilm bacteria activate the acute phase hepatic response which further increases the total count of leukocytes and other inflammatory markers which can predispose the patient to systemic diseases [21,31]. These mediators, along with bacteria and their products, can play a significant role in the pathogenesis of atheroma and thrombus formation. Thus, Offenbacher et al. [41] suggest that both diseases can constitute a syndrome which would stand for “periodontitis-atherosclerosis syndrome”. The mechanism involved in this syndrome is the inflammatory reaction caused by the oral biofilm in the periodontal tissues, and its potential consequences.

The mechanisms by which periodontitis contributes to CVD have not been confirmed, but there are numerous working hypothesis that will be proved or disproved [42]. Poor oral health and coronary heart disease are major worldwide health problems, and their associations are potentially important.

So, the results suggest that periodontal infection might be one of the underdiagnosed chronic inflammations contributory to systemic inflammatory respons, which in turn may increase the risk for CVDs. Those who suffered from periodontitis demonstrated a significantly higher incidence of coronary heart disease and premature death [8]. The more severe periodontal inflammation as supported in this study, may lead to lipid metabolism disturbance and a hipercoagulable state elevating circulating cytokines. Therefore, changes in this marker in periodontitis may be part of the explanation why periodontitis is associated with cardiovascular diseases. It is hypothesized that possibly daily episodes of a bacteremia originating from periodontal lesions are the cause for the changes in systemic markers in periodontitis [43,44].

It is also noteworthy that there may be other potential pathways underlying the association between periodontitis and increased CVD risk and more studies are needed to clarify the role of periodontitis in the aetiology and development of CVD. Thus, it is possible that these CVD risk factors may serve as intermediate variables linking periodontal disease to eleveted CVD risk.

Periodontitis with all its clinical symptoms and consequences can pose a potential risk of systemic exposure to inflammatory stress with increased values of the markers of inflammation (leukocytes and neutrophils, CRP, and fibrinogen), and thus create a close connection with the systemic status of the patient [45,46].

Finally, these findings suggest the necessity for further investigations regarding the association between

periodontitis and systemic diseases, particularly a possible influence of periodontal therapy on the reduction of the mediators of inflammation, which would possibly decrease the risk of systemic diseases.

5. Conclusion

In conclusion, the analysis of the data presented in this paper confirms the concept that the increase in the total counts leukocytes and neutrophiles in the patients with chronic periodontitis, especially its severe form, can be the indicator of possible exposure of an organism to some systemic disease.

Futher, plasma levels of acute-phase proteins (CRP and fibrinogen) are associated with periodontitis in periodontitis patients depends on the severity of disease after adjusting for age and BMI.

In addition, it should be a warning to doctors treating systemic diseases (cardiologists, doctors of internal medicine, etc.) to refer their patients to a dentist, that is a specialist in periodontology. Measures that can be implemented to improve oral health include definitive treatment of periodontitis, regular visits to a dental proffessional for toothcleaning, and improved oral hygiene.

Statement of Competing Interests

The authors declare that they have no any financial support and any conflict of interest.

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