Original Article

The influence of diabetes and or periodontitis on inflammation and adiponectin level

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ABSTRACT

Background: In Indonesia, most of diabetic patients had periodontitis and 75.3% of them had severe periodontitis. Previous study found that hyperglycemia and or local inflammation (such as periodontitis) modulated systemic pro-inflammatory and anti-inflammatory cytokines.
Aims: This study aimed to investigate the effect of DM and or periodontitis on systemic cytokines and adipocytokines levels.
Methods and materials: A total of 57 participants with age of 29−71 years were recruited for this study. We divided them into three groups; DM-periodontitis (n = 22), periodontitis without DM (n = 16) and control (n = 19). All participants underwent physical examinations (BMI, WC, periodontal status examination) and laboratory examinations (FBG, fasting insulin, CRP, adiponektin, leptin, TNF-α and IL-10).
Results: The proportion of severe periodontitis were higher in DM-periodontitis group compared to periodontitis without DM (77.3% vs 6.2%). DM-periodontitis group had lower adiponectin levels than that of periodontitis without DM group [5860.78 ± 4182.40 vs 9553.13 ± 6794.73; p = 0.046]. TNF-α/IL-10 ratio was significantly higher in the periodontitis without DM compared to control group [1.96 (1.68 −2.32) vs 1.55 (1.27−1.85); p = 0.015].
Conclusion: Local inflammation such as periodontitis, elevated systemic inflammatory markers (TNF-α/ IL-10 ratio). Meanwhile chronic hyperglycemia alter adipocytokines level. The changes of systemic inflammation among diabetic group had not been shown yet in this study since some antidiabetic and antilipid drugs possess anti-inflammtory effect. Age, WC and FBG correlated with severe periodontitis. Adiponectin, leptin, TNF-α and IL-10 levels did not correlated with severe periodontitis.

1. Background

Diabetes Mellitus (DM) is a progress systemic disease characterized by chronic hyperglycemia. Defects in pancreatic b cell producing insulin, decrease in insulin sensitivity or combination of both are leads to failure of blood glucose regulation [1−3]. DM currently is the 12 leading causes of death, with estimated prevalence of DM 220.5 million or 2.8% of the population worldwide [4]. In Indonesia the prevalence of DM in 2008 was 5.7% and become top 10 countries with the most DM patients in the world [2].

Hyperglycemia induce systemic inflammation marked by increased inflammatory markers like C-reactive Protein (CRP), Interleukin-6 (IL-6) and Tumor Necrosis Factor Alpha (TNF-α). TNF-α is a major signal of cellular apoptosis, bone absorption, secretion of Matrix Metalloproteinase (MMP), expression of Intercellular Adhesion Molecule (ICAM) and increased production of IL-6 [5]. Increased pro-inflammatory markers are followed by decreased production and response of anti-inflammatory markers. Interleukin-10 (IL-10), the most studied anti-inflammatory cytokine, decreased in DM. In an experimental study IL-10 failed to suppress TNF-α in the blood culture of DM [6]. Hyperglycemia can interfere neutrophil function, cause lowering chemotactic activity, ability of phagocytosis and bactericidal against bacteremia, thus increasing the severity of infection in diabetic patients [7,8].

Beside alteration of pro-inflammatory and anti-inflammatory

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cytokines, diabetic patients exposed adipose tissue dysfunction due to obesity induced insulin resistance [9]. The two main adipokines linked to insulin resistance and DM are adiponectin and leptin. Adiponectin exposed anti-inflammatory effect by reducing the activation of Nuclear Factor Kappa B (NF-$_K$B), while leptin is pro-inflammatory adipokine that influence pro-inflammatory T cells [10].

Periodontitis is a chronic inflammation in supporting tissues around the teeth known as periodontium [11–13]. Inflammation of the gingival tissue or asymptomatic gingivitis was the first manifestation of periodontal disease. This condition can return to normal if patient maintain the oral cavity hygiene. However, if the condition continues it will become periodontitis [11]. Persistence condition of local inflammatory periodontitis can affect systemic health and increasing the risk of several chronic diseases [14].

Periodontal disease and DM have a close relationship and both are chronic diseases with high prevalence. DM patients have a greater risk of 2–3 times for periodontitis [15]. Poor glycemic control increased gingival inflammation and the severity of periodontitis, whereas periodontitis risks increasing blood glucose [16]. Jansson et al. showed that patients with periodontitis had higher HbA1c levels (p = 0.033) and higher prevalence of myocardial infarction (p = 0.012) than that of without periodontitis [17]. DM patients with periodontitis is related to changes in the immune system, glucose accumulation in periodontal tissue, demage of periodontal blood vessel, increased proteolysis and osteolysis from the structure periodontal, increased concentration of pro-inflammatory cytokines, reduced regeneration of collagen structures and development of pathogens in the mouth [15].

Study by Al-azawy et al. in Iraq showed periodontitis patients with DM had lower adiponectin levels (p < 0.001) and higher leptin levels (p < 0.01) compared to periodontitis patients without DM and healthy controls [18]. Acharya et al. in India showed that periodontitis patients with T2DM would have higher levels of TNF-α and IL-6 compared to periodontitis patients without DM and healthy controls (p < 0.05)[19], whereas IL-10 levels were found to be significantly lower in patients with periodontitis and T2DM was compared with healthy control patients in the Acharya et al. study of IL-10 (p < 0.05) [20].

Studies regarding the effect of local inflammation on systemic inflammatory markers in DM is limited. Previous studies reported different result due to heterogenicity of subject characteristic. Since periodontitis is the one of the most common local infection in DM, this study tried to evalute the profile of systemic pro-inflammatory, anti-inflammatory and adipocytokine among diabetic patients with periodontitis.

2. Material and methods

As many 57 subjects with age of 29–71 years were recruited and divided into three groups: DM with periodontitis (n = 22), periodontitis (n = 16) and healthy subjects without DM and periodontitis (n = 19) as the control group. Subjects with autoimmune diseases, Chronic Kidney Disease (CKD) stage ≥ 3 or more, chronic infectious or inflammatory diseases other than periodontitis, pregnancy and ongoing antimicrobial users were excluded in this study. This research has passed the Faculty of Medicine Universitas Indonesia (FMUI) ethical review with number 130/UN2·F1/ETIK/ 2017. Data collection was carried out consecutively in the Polyclinic of Dental and oral Disease Cipto Mangunkusumo National Referral Hospital/Cipto Mangunkusumo Hospital (CMH), Jakarta, Indonesia.

Subjects who agreed to participate in this study and signed an informed consent will take an interview, physical examination and laboratory examination. Physical examination consist of measurements of blood pressure, weight, height, calculation of Body Mass Index (BMI) [body weight (kg)/height [2] (m²)], Waist Circumference (WC) and periodontal status examination.

2.1. Periodontology examination

Periodontal status examination is performed by two certified periodontology consultant dentists. Respondents underwent oral examinations with the Aesculap® DB874R periodontal probe. We assessed Pocket Depth (PD), Clinical Attachment Loss (CAL), Bleeding on Probing (BOP) and Plaque Index (PI). PD is the distance between the gingival margin and the pocket base. CAL is assessed by looking at cemento-enamel junctions. BOP is assessed based on Saxer and Muhlemann classifications. The BOP value is obtained from the total value for the number of places examined. Oral hygiene was assessed by PI based on Sillness and Loe classifications. The final value is obtained from the total value divided by the number of teeth examined. Based on the CAL values classified from the 1999 American Academy of Periodontology Criteria, all subjects were divided into (1) CAL 1–2 mm: mild periodontitis, (2) CAL 3–4 mm: moderate periodontitis and (3) CAL> 5 mm: severe periodontitis. In this study we divided the periodontitis criteria into two groups, severe and non severe (mild-moderate periodontitis).

2.2. Laboratory examination

Laboratory tests were carried out in the clinical pathology laboratory CMH and integrated laboratories FMUI. After overnight fasting for 10–12 h, all participants underwent blood sampling. Laboratory tests include Fasting Blood Glucose (FBG), fasting insulin, quantitative CRP, adiponectin, leptin, TNF-α and IL-10. These inflammatory markers meassured by ELISA method (IL-10: Human IL-10 Quantikine Elisa Kit [R & D]; TNF-α: Human TNF Alpha Quantikine [R & D]; adiponectin: Human Total Adiponectin/Acrp30 Immunoassay [R & D]; leptin: Leptin Elisa Kit [DRG]). To detect insulin sensitivity we evaluated Homeostasis Model Assesment for Insulin Resistance (HOMA-IR) using the following formula: (fasting insulin in mU/l x FBG in mmol/l) divided by 22.5 and to evaluate pancreatic β-cell function we meassured Homeostasis Model Assesment for β-cell function (HOMA-B) by formula: (20 x fasting insulin in mU/l) divided by (FBG in mmol/l − 3.5).

2.3. Statistical analysis

Statistical analysis using SPSS 21.0. Distribution data was analyzed by the Kolmogorov-smirnov normality test. Data with abnormal distribution is calculated by log 10 to normalize data. Data are presented with mean/median (standard deviation (SD)/ interquartile range (IQR)). Bivariate analysis using an independent t-test for normal data distribution, and using Mann Whitney Test for abnormal data distribution. The correlation between several parameter and severity of periodontitis we meassured by linear regression.

3. Results

A total of 57 subjects were divided into 3 groups, DM-periodontitis, periodontitis without DM and control group. Subject characteristics in each group can be seen in Table 1. The majority of subjects were female, aged of 40–50 years. DM-periodontitis group had the highest BMI compared to two other groups even though it was not statistically significant. DM-periodontitis group had the highest insulin resistance (HOMA-IR) value (6.76 mIU/L) and the lowest β-cell function (105.6%) compared to the other two groups, along with the highest blood glucose level. Severe periodontitis is more common in the DM-

Table 1
Baseline characteristic of the subjects.

Variable	DM-Periodontitis (n = 22)	Periodontitis without DM (n = 16)	Control (n = 19)
Age	49.5 (8.78)	50.81 (12.50)	40.53 (10.59)
BMI	26.32 (3.54)	24.87 (4.83)	24.56 (3.92)
WC	93.64 (8.75)	85.06 (15.11)	85.74 (12.59)
Gender (%)			
Men	7 (31.8)	5 (31.2)	7 (36.8)
Women	15 (68.2)	11 (68.8)	12 (63.2)
FBG	128.0 (99.75—148.75)	89.0 (86.25—95.50)	91 (86.00—93.00)
Fasting Insulin	17.77 (24.08)	8.81 (6.68)	11.18 (4.91)
HOMA-IR	6.76 (11.70)	2.00 (1.56)	2.51 (1.19)
HOMA-B	105.6 (114.4)	114.8 (89.12)	153.4 (61.02)
CRP	1.55 (.58—3.13)	2.00 (1.25—3.00)	1.90 (.60—5.00)
Duration of DM (year)	6 (3.75—13.00)	—	—
Periodontitis severity (%)			
Severe	17 (77.3)	1 (6.2)	
Non severe	5 (22.7)	15 (93.8)	—

periodontitis group (77.3%) than in the periodontitis without DM group (6.2%).

In bivariate analysis of inflammatory markers and adipocytokines between 2 groups (DM-periodontitis vs Periodontitis without DM), there was significantly lower adiponectin levels in the DM-periodontitis [5.88 ± 4.18] compared to periodontitis without DM [9.55 ± 7.96; p = 0.046], meanwhile leptin levels in DM-periodontitis were higher [5.64 ± 4.42] compared to periodontitis without DM but was not significant [5.26 ± 4.30; p = 0.792], and leptin/adiponektin ratio was lower in DM-periodontitis compared to periodontitis without DM [1.09 (0.37—2.39) vs 0.36 (0.24—1.22); p = 0.084]. IL-10 cytokines were higher insignificant in the DM-periodontitis than in the periodontitis without DM (6.98 ± 12.63 vs 3.38 ± 1.05; p = 0.079), whereas TNF-α and TNF-α/IL-10 ratio were higher insignificant in the periodontitis without DM compared to DM-periodontitis.

In periodontitis without DM group, we found higher adiponectin levels, lower leptin and higher leptin/adiponektin ratio than that of control group, although the difference was not significant (Table 2). Cytokines level in this analysis obtained higher IL-10 and lower TNF-α insignificant between the periodontitis without DM and control group. Meanwhile TNF-α/IL-10 ratio was significantly higher in the periodontitis without DM compared to the control group [1.96 (1.68—2.32) vs 1.55 (1.27—1.85); p = 0.015].

Comparisons between DM-periodontitis and the control did not show any significant differences in all examination parameters. However, adipokine analysis showed lower adiponectin, higher leptin and higher leptin/adiponektin ratio in DM-periodontitis compared to the control group. DM-periodontitis had higher IL-10, TNF-α, and TNF-α/IL-10 ratio than that of the control group (Table 3).

Table 4 report the linear regression analysis of correlation between several parameter and severity of periodontitis. Age, WC and FBG levels had a significant effect on the incidence of severe periodontitis (p = 0.007; 0.030; 0.000). Meanwhile there was no correlation between adiponectin, leptin, TNF-α and IL-10 with the incidence of severe periodontitis (p = 0.929, 0.908, 0.092, 0.241).

4. Discussion

Several study has been conducted on inflammatory markers and adipokines in periodontitis with or without DM with diverse results. The periodontal condition begins with the invasion of microorganisms in epithelial cells and stimulate to secrete various inflammatory mediators into gingival crevicular fluid (GCF) [21]. Periodontal inflammation can affect the composition of pro-inflammatory GCF biomarkers level [22]. Several studies used GCF specimens to see inflammatory markers (IL-1β, IL-6 and TNF-α) and adipocytokines (adiponectin and leptin). This method was performed to show local inflammation [21,23,24]. Karthikeyan et al. used GCF specimens and blood serum in their study, and showed that periodontitis group possess lowest leptin levels in GCF and highest leptin serum compared to healthy control and gingivitis group [25]. In this study we used blood specimen to evaluate the influence of local inflammation (periodontitis) among periodontitis with and without DM and control group to systemic inflammation and adipocytokines changes. To the best of our knowledge, this was the first study in Indonesia regarding the inflammatory markers and adipocytokines in periodontitis with or without DM using blood serum specimens.

This study involved DM patients with a wide age range between 29 and 71 years, the majority of age range between 40 and 50 years. Meanwhile previous studies limited the research subjects in the age range between 30 and 55 years. This wide age range can affect cytokine and adipocytokine profiles [26,27]. In this study, the subjects were mostly female in three groups. This can minimize the influence of sex on inflammatory and adipocytokine markers. In contrast to this study, the study of Al-Azawy et al. in Iraq has differences in sex distribution among the three groups. In the Al-Azawy study, DM-peridontitis group was dominated by female, while the group of periodontitis without DM and controls were dominated by male [18]. Sex influence the profile of cytokines and adipocytokines, whereas male subjects tend to have lower leptin/adiponectin ratio compared to females [28,29].

DM-periodontitis group had the highest BMI and WC compared

Table 2
Profile of inflammation and adipocytokine levels among 3 groups.

	Adiponektin	Leptin	IL-10	TNF-α	Leptin/adiponektin	TNF/IL-10
DM-periodontitis (n = 22)	5.88 (4.18)	5.64 (4.42)	6.98 (12.63)	6.16 (5.43—12.94)	1.09 (0.37—2.39)	1.92 (1.38—2.31)
Periodontitis without DM (n = 16)	9.55 (7.96)	5.26 (4.30)	3.38 (1.05)	6.52 (5.13—8.10)	0.36 (0.24—1.22)	1.96 (1.68—2.32)
Control (n = 19)	6.38 (4.86)	5.84 (4.00)	3.84 (1.14)	5.47 (5.30—6.16)	1.07 (0.40—1.42)	1.55 (1.27—1.85)

Mean/Median [Standar Deviation(SD)/Interquartile Range (IQR)].

Table 3
Correlation of inflammation and adipocytokine level between two groups.

	Adiponektin	Leptin	IL-10	TNF-α	Leptin/adiponektin	TNF/IL-10
DM-periodontitis vs Periodontitis without DM	.046[a*]	.792[a]	.079[a]	.722[b]	.084[b]	.529[b]
Periodontitis without DM vs control	.115[a]	.678[a]	.195[a]	.091[b]	.109[b]	.015[b*]
DM-periodontitis vs control	.714[a]	.877[a]	.230[a]	.061[b]	.774[a]	.123[b]

[a] Independent T-Test; b. Mann-Whitney T-Test; *p-value < 0.05.

Table 4
Correlation of clinical factors, inflammation, and adipocytokine level to the severity of periodontitis.

beParameter	R	p-value
Age	0.351	0.007[d*]
BMI	0.184	0.172[d]
WC	0.288	0.030[d*]
Gender	0.015	0.910[c]
FBG	0.551	0.000[c*]
Fasting Insulin	0.063	0.641[d]
Homa-IR	0.158	0.112[d]
Homa-B	0.257	0.053[d]
CRP	0.158	0.241[c]
Adiponektin	0.012	0.929[d]
Leptin	0.016	0.908[d]
IL-10	0.158	0.241[d]
TNF-α	0.225	0.092[c]

[c] Spareman, d. Pearson *p-value < 0.05.

to periodontitis without DM and the control group (BMI values: 26.32 ± 3.54 vs 24.87 ± 4.83, 24.56 ± 3.92) (WC values: 93.64 ± 8.75 vs. 85.06 ± 15.11, 85.74 ± 12.59). This result similar with the previous study by Ling et al. who reported that DM-periodontitis group had the highest BMI compared to periodontitis and healthy control [30]. Obesity interferes adipocytokine profile which is characterized by decrease in adiponectin and increase in leptin levels [31]. Obese populations and individu with central obesity also tend to had higher inflammatory marker (TNF-α) than in populations with ideal body weight [32].

4.1. Proportion of severe periodontitis

Blood glucose dysregulation in DM can affect macrovascular and microvascular conditions, including periodontal tissue. Some studies have found a significant relationship between hyperglycemia with periodontal disease in people with DM [8,17,33—35]. Occurrence of periodontitis in people with DM is associated with microvascular complication, impaired neutrophil function, collagen synthesis, microbiotic factors and genetic factors. Emor et al. in Indonesia showed high proportion of severe and moderate periodontitis among diabetic patient (56.8% and 43.2%) and non of the diabetic patients had good periodontal status [8]. This is consistent with our study that DM-periodontitis group had the worst periodontal status which is characterized by the very high proportion of severe periodontitis [17 (77%)] compared with periodontitis without DM group [1 (6.2%)]. Periodontitis is one of the most common local inflammation found in community including diabetic patients. Previous study reported the correlation between GCF and serum inflammatory cytokine in diabetic patients with periodontitis, which mean that local inflammation contribute to change systemic inflammation. Thus any inflammation or infection in diabetic patients give an increase risk of worse glycemic control and chronic complication [25].

4.2. Inflammation cytokine proflie (TNF-α and IL-10)

Insulin resistance in T2DM patients is associated with chronic inflammation and impaired adipocytokine production. Both of them increase risk of endothelial dysfunction and metabolic disorders in T2DM. TNF-α is a pro-inflammatory cytokine that increase in T2DM [10,36]. Meanwhile IL-10 is an anti-inflammatory cytokine, which can decrease or increase in T2DM. The derivation of IL-10 in DM was reported through the mechanism of T cell and B cell disruption, whereas IL-10 increases due to monocyte stimulation. In the other hand, IL-10 in T2DM was less effective at inhibiting TNF-α secretion, characterized by an increase in TNF-α [6,10].

In this study there were no significant differences of TNF-α levels and TNF-α/IL-10 ratio between DM-periodontitis and periodontitis without DM. In DM-periodontitis group, TNF-α levels were lower not significant compared to the periodontitis without DM group [6.16 (5.43—12.94) vs 6.52 (5.13—8.10); p = 0.722]. TNF-α levels can be affected by drugs taken by DM patients, such as metformin and statin groups. Beside being a therapy for hyperglycemia, metformin can reduce inflammation and oxidative stress. Animal study by Hyun B et al. showed that metformin can reduce Nitric Oxide (NO) secretion, Prostaglandin E_2 (PGE_2), and pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) by decreasing $NF-_KB$ regulation on macrophages. Metformin also improve anti-inflammatory cytokines such as IL-4 and IL-10 [37]. Another study by Andrews et al. in 30 patients with non-insulin T2DM showed that metformin group had reduced CRP and TNF-α levels compared to non metformin group [38]. Atorvastatin also can reduce TNF-α expression and production by inhibiting the influence of lipopolysaccharide (LPS) on macrophages [39]. Our finding showed different result with Acharya et al. He reported significantly higher TNF-α levels in DM-periodontitis than that of periodontitis without DM. Acharya study matching age and sex between the four groups (DM-periodontitis, periodontitis without DM, DM without periodontitis and control), and limiting the study subjects with BMI <30 kg/m^2. The method of subjects selection may reduce the influence of age, sex, and BMI on cytokines level. It might explain the differences results between Acharya's study and this study [19].

Interleukin-10 level were higher in the DM-periodontitis than that of in periodontitis without DM, although it was not statistically significant [6.98 ± 12.63 vs 3.38 ± 1.05; p = 0.079]. Several studies have shown the failure of anti-inflammatory cytokines response to inflammatory conditions in DM patients. Increased IL-10 in DM group can show local inflammatory stimulation of monocyte cells. Monocytes can also secrete IL-10 but in DM patient this response has not been able to overcome the failure of secretion of IL-10 by lymphocyte cells (T cells and B cells) [10]. In addition, increased IL-10 in the DM-periodontitis group can influenced by the effects of drugs such as metformin [37]. Beside drugs effect, IL-10 level can increased due to reduced superoxide anion generation resulting in improved NO bioavailability [40]. These findings support the study of Acharya et al. which reported that IL-10 level in DM-periodontitis was higher insignificant than that of periodontitis

without DM [11.35 ± 0.97 vs. 10.50 ± 0.61; p = 0.374] [20].

Periodontitis without DM had higher TNF-α levels and lower IL-10 levels than that of control group even though they were not statistically significant. This results support a study by Shaker et al. in Iraq, which showed significantly higher TNF-α and lower IL-10 in patients periodontitis without DM than in control group. Meanwhile our study found TNF-α/IL-10 ratio had significantly higher values in periodontitis without DM compared to control group [1.96 (1.68−2.32) vs 1.55 (1.27−1.85); p = 0.015]. This is in accordance with the study by Shaker which showed higher TNF-α/IL-10 ratio in periodontitis patients than control [42.72 (0.35−53.46) vs. 28.56 (0.55−43.46); p = 0.008]. The TNF-α/IL-10 ratio is expected to show the interaction between pro-inflammatory and anti-inflammatory activities [41]. The balance of TNF-α and IL-10 is important for maintaining immune homeostasis. Rapid TNF-α production results in severe inflammatory responses and tissue damage. However, an increase in TNF-α was followed by the simultaneous synthesis of anti-inflammatory cytokines IL-10, which suppresses production of many activating and regulatory mediators [42]. Previous studies stated that TNF-α/IL-10 ratio correlated with severe inflammation as burn and myocardial infarction [40,43].

The analysis result of pro-inflammatory and anti-inflammatory cytokines in this study showed the effect of periodontitis as a local infection that changes inflammatory cytokines in peripheral blood (systemic). The early stages of periodontal disease in local response was increases the synthesis of cytokines and inflammatory mediators which cause destruction of periodontal ligaments and supportive bones. If the condition of this periodontitis continues, it can cause a systemic response and cause a variety of systemic diseases such as cardiovascular disorders, stroke, respiratory disease and pregnancy problems [44]. In addition, bacteria that develop in periodontal tissues can also enter the circulation and affect systemic inflammation, causing infection directly (bacteremia, endocarditis) or a reaction to bacterial antigens with host antibodies [45].

4.3. Adiponektin and leptin profile

Obesity and T2DM can caused a decrease in adiponectin and increase in leptin levels. Adiponectin is an anti-inflammatory, while leptin is a pro-inflammatory [10]. This study found significantly lower adiponectin level in DM-periodontitis compared to periodontitis without DM [5860.78 ± 4182.40 vs 9553.13 ± 6794.73; p = 0.046], and insignificant higher leptin levels in DM-periodontitis compared to periodontitis without DM [5.64 ± 4.42 vs. 5.26 ± 4.30; p = 0.792]. This finding is consistent with the study of Al-azawy et al. in Iraq that showed adiponectin levels were lower (p < 0.001) and higher leptin levels (p < 0.01) in T2DM patients and periodontitis compared with periodontitis without DM [18]. Patients with DM were related to fat accumulated, thus suggested to produce excessive free radical and oxidative stress. Furthermore may lead to dysregulation of adipocytokine (leptin, adiponektin and resistin) and inflammatory mediators (plasminogen activator inhibitor−1/PAI-1, TNF-α and IL-6). Leptin can promote but adiponectin prevent the formation of insulin resistance, thus leptin/adiponectin ratio may be a predictor of insulin resistance [46]. Adiponectin and leptin not only affect the insulin sensitivity, but also involved in inflammatory process, this biomarker can be a prediction of chronic inflammations [30].

Our study did not find significant differences of adiponektin, leptin and leptin/adiponectin ratio between DM-periodontitis and control group also between periodontitis without DM and control group. There was difference of age distribution between three groups. The control group had the lowest age compared to DM-periodontitis and periodontitis without DM groups. During this study it was not easy to find healthy subjects without periodontitis above 40 years of age. The effect of age on body fat distribution is believed to influence adipocytokine profile secreted by adipose tissue. This is thought to affect the profile of adiponectin, leptin and the leptin/adiponektin ratio in three groups.

In addition to age, the presence or absence of hyperglycemia is thought to affect changes in adipocytokine levels. In this study, the control group had lower adiponectin levels and higher leptin compared to periodontitis without DM although it was not significant. There are several factors that influence adiponectin and leptin that were not evaluated in this study like diet pattern, physical activity and body composition. Rokling-Andersen et al. stated that dietary interventions significantly influence the increase in adiponectin levels (p = 0.03), this can be explained because diet regulation can change the body fat [47]. Yu et al. in China stated that high physical activity is related to better adipocytokine and inflammatory factors and can reduce the risk of metabolic syndrome events (OR 0.68; 95% CI 0.54−0.85; p = 0.001) [48].

4.4. Several factors that correlate with severe periodontitis

In further analysis we assessed the correlation between age, BMI, WC, gender, FBG, fasting insulin, HOMA-B, HOMA-IR, CRP, adiponectin, leptin, IL-10, TNF-α and severe periodontitis. Our analysis obtained that age (p = 0.007), WC (p = 0.030) and FBG (p = 0.000) correlated with severe periodontitis. This is consistent with a study from Francis et al. which said that there was a significant relationship between age and severe periodontitis (p < 0.001) [49]. Kangas et al. in their study showed that WC was associated with a deeper risk of PD (PD > 4 mm) (OR 1.5, CI: 1.2−1.9) [50]. Several previous studies conducted in India [33], Sweden [17] and Indonesia [8] showed that hyperglycemia in DM was associated with the onset of periodontitis. The correlation between adiponectin and leptin serum with severity of periodontitis in this study were insignificant. Al-azawy et al. supported this finding, which stated that adiponectin and leptin serum did not observe significant correlation with clinical periodontal parameters [18].

4.5. Limitation of the study

In this study, the researcher did not matched the age between three groups. At the end of the study the control group had youngest age averages compared to DM-periodontitis and the periodontitis without DM group. This study also did not limit the BMI range. People with severe obesity (BMI > 30 kg/m^2) had different inflammatory cytokine and adipocytokine profiles compared to people with BMI <30 kg/m2. This factor can influence the analysis of differences in cytokines and adipocytokines levels among the three groups.

5. Conclusion

Local inflammation such as periodontitis, elevated systemic inflammatory markers (TNF-α/IL-10 ratio). Meanwhile chronic hyperglycemia alter adipocytokines level. The changes of systemic inflammation among diabetic group had not been shown yet in this study since some antidiabetic and antilipid drugs possess anti-inflammtory effect. Age, WC and FBG correlated with severe periodontitis. Adiponectin, leptin, TNF-α and IL-10 levels did not correlated with severe periodontitis.

Acknowledgment

List of abbreviations

DM	Diabetes Mellitus
CRP	C-reactive Protein
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor Alpha
MMP	Matrix Metalloproteinase
ICAM	Intercellular Adhesion Molecule
IL-10	Interleukin-10
NF-κB	Nuclear Factor Kappa B
CKD	Chronic Kidney Disease
FMUI	Faculty of Medicine Universitas Indonesia
CMH	Cipto Mangunkusumo Hospital
BMI	Body Mass Index
WC	Waist Circumference
PD	Pocket Depth
CAL	Clinical Attachment Loss
BOP	Bleeding on Probing
PI	Plaque Index
FBG	Fasting Blood Glucose
HOMA-IR	Homeostasis Model Assesment for Insulin Resistance
HOMA-B	Homeostasis Model Assesment for β-cell function
SD	Standard Deviation
IQR	Interquartile Range
GCF	Gingival Crevicular Fluid

Ethics approval and consent to participate

This study has been approved by the ethic committee of Faculty of Medicine Universitas Indonesia (No 130/UN2·F1/ETIK/2017). Informed consent was obtained from all enrolled study participants.

Consent for publication

All authors consent to publish this study. The authors guarantee that any data of this study has not been published anywhere else as a whole or in part. All authors have declare to approve the publication of this study and any person named as co-author is aware and agreed of the publication and the order authors naming.

Availability of data and material

The authors confirm that the data supporting the results of this study are available within the article.

Competing interest

The authors declare that they have no competing interest.

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Author contributions

Idea, study design, article draft writing: DP and AIK; Data collection and analysis: YS and SM.

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