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Periodontitis correlated with increased ESR and platelet counts in Indonesians with type 2 diabetes mellitus

Hendri Susanto,[1*] Frank Abbas[2]

Abstract

Objective: To assess the correlation between periodontitis, systemic inflammatory markers and platelet counts in Indonesian DM2 patients.
Material and Methods: A full mouth periodontal examination including bleeding on probing, probing pocket depth, gingival recession, and plaque scores was performed in Indonesians DM2 in Dr. Sardjito Hospital, Yogyakarta. Indonesia. In addition, glycated hemoglobin (HbA1c), erythrocyte sedimentation rates (ESR), High sensitivity C reactive protein (Hs-CRP), peripheral blood counts, were assessed. To assess age, body mass index (BMI) education level, ethnicity, sex/gender, smoking, a standardized questionnaire was used and presented descriptively. In correlation and multiple linear regression analyses, it was assessed whether periodontitis operationalized with periodontal inflamed surface area (PISA) correlated with systemic inflammatory markers (Hs-CRP, ESR), HbA1c and peripheral blood counts (hemoglobin, leucocytes, erythrocytes, platelets, hematocrite) with 95% Confidence Interval.
Results: In 44 Indonesians treated for DM2, PISA was associated with ESR ($r = 0.32$; $p<0.05$), and platelet count ($r = 0.527$; $p < 0.05$). Plaque score and PISA were the predictors for platelet count ($p<0.05$)
Conclusion: Periodontitis Is associated with increased the systemic inflammation marker Erythrocyte Sedimentation Rate (ESR) and platelet counts in Indonesians DM2 and therefore may form an additional risk factor for atherosclerosis in these patients.

Keywords: Periodontitis (MeSH); PISA; type 2 diabetes mellitus (MeSH); ESR, platelet count (MeSH)
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Introduction

The prevalence of DM in South East Asia Region is 5.3%.[1] The prevalence of DM in Indonesia still increases and putting Indonesia in the top ten of the highest number DM patients in the world., It is estimated the number of patients with DM in Indonesia will be over 20 millions by the year 2030 (approximately 10% of the population).[2,3] Our previous study showed that Indonesians with DM2 have a higher prevalence of periodontitis than healthy controls with this high and rising prevalence of DM2 in Indonesia, periodontitis prevalence and severity may also rise. As a consequence of the bilateral causal association between periodontitis and DM2, a rising periodontitis prevalence and severity in DM2 patients, may give rise to further deterioration of DM2 and thus increase the complications of DM2. Microangipoathy and macroangipathy are the most complications of DM2 which is caused by atherosclerosis.[4,5] Atherosclerosis may be mediated by the increase of systemic inflammation which caused by periodontitis and poor controlled blood glucose, high HbA1c, in DM. A vicious circle may arise in which poor control of blood glucose which indicating by the high HbA1c, causes a deteriorating periodontal condition, which in turn causes further deterioration of blood glucose control, then long standing poor controlled blood glucose and untreated periodontitis may increase the atehrosclerosis in DM.[6]

Numerous systemic inflammation markers have been known related with periodontitis and DM2. C-reactive protein (CRP) is one of the important systemic inflammation markers that would be involved in atherosclerosis in DM and also induced by periodontitis.[5-9] Our previous study revealed that periodontitis inflamed surface area (PISA) and CRP were predictors for blood glucose regulation (HbA1c) in Indonesians healthy and DM2. Moreover, periodontal treatment also contribute to decrease systemic inflammation markers (CRP) in DM2.[10-13] Besides, non-specific systemic inflammation markers, erythrocyte sedimentation rate (ESR) also increased in periodontitis and DM2. Moreover, periodontal treatment has been known also reduce ESR in periodontitis.[14] The increased risk of atherosclerosis in DM2 may be also caused by the increased of platelet number which contribute to blood clot formation in blood vessel. Both systemic inflammation and increase of platelet number may increase the risk factor for atherosclerosis. Then, the atherosclerosis may increase the risk factor for life threatening complication of DM2 such as cardiovascular diseases. A study revealed that platelet

[1]Department of Oral Medicine, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia
[2]University Medical Center Groningen-Center for Dentistry, University of Groningen, The Netherlands

Correspondence to: Hendri Susanto. Department of Oral Medicine, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, Indonesia
drghendri@ugm.ac.id

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number was increased in periodontitis patients which indicating that the high risk systemic inflammation in periodontitis.[15] Hence, the increased platelet number may associate with the atherosclerosis and cardiovascular diseases. However, in different populations also different association patterns may occur. Consequently, the purpose of the present investigation was to study whether periodontitis was associated with increased ESR and platelet numbers in DM2 in Indonesia.

Material and Methods

DM2 patients who were treated for DM2 were asked to participate in this study. All DM2 patients had been diagnosed by specialist internist of Internal Medicine Dept. Dr. Sardjito Hospital, Yogjakarta according to World Health Organization criteria: fasting blood glucose level ≥126 mg/dl and/or a postprandial blood glucose level ≥200 mg/dl.[16] The inclusion criteria, DM2 patients did not wear dentures, did not have another systemic diseases and non edentulous. All participants was screened for other systemic diseases using a validated general health assessment questionnaire for.[17]to develop such a history (EMRRH The original questionnaire was translated from English into Indonesian to validate the questionnaire for Indonesia. To check for potential differences, a reverse translation to English was made, and no substantial differences were found. Written Informed consent was obtained from all participants. The study was approved by the Ethical Committee for Research of the Medical Faculty of Universitas Gadjah Mada (Ref:KF/FK/206/EC).

In DM2 patients who gave informed consent, a full mouth periodontal screening was carried out: bleeding on probing (BOP)_measurements, periodontal probing pocket depth (PPD), gingival recession, plaque score was performed on all teeth on six sites per tooth. All permanent fully erupted teeth were examined using a colour coded standard periodontal probe, (Dentsply, London, UK). BOP is bleeding recorded as either present or absent of probing at 6 sites per tooth within 30 seconds. Plaque score is defined as plaque being present or absent at 6 points on each tooth. The missing teeth was also recorded.[18] The Clinical Attachment Level (CAL) (calculated as the sum of the probing pocket depth and gingival recession measurements) > 3, > 4, > 5 and > 6 mm, mean CAL, mean PPD , percentage of sites with bleeding on probing (BOP).[19]

Additionally, to determine the amount of periodontitis the Periodontal Inflammed Surface Area (PISA) which reflects the surface area of *bleeding* pocket epithelium in square millimetres was calculated. PISA was calculated using conventional BOP measurements and CAL and gingival recession. PISA quantifies the amount of inflamed periodontal tissue, and it is suggested that PISA thereby quantifies the inflammatory burden of periodontitis in DM2.

A blood sample was obataned form all participants using a venipuncture for peripheral blood parameters (hemoglobin, Leucocytes, Eryhtrocytes, Platelets, Hematocite). Glycosilated/glycated hemoglobin (HbA1c) values was measured using low pressure cation ion exchange chromatography (DIASTAT™, Bio-Rad, USA), ESR was determined by Westergren, and CRP determined by a high-sensitivity chemiluminescent immunometris assay (Immulite 2000™, Diagnostic Products Corp., Los Angeles, CA, USA), were determined for all participants.

Statistical analysis

The demographic characteristic of subjects such as age, Body Mass Index (BMI), Education level, sex/gender, smoking status, and ethnicity, number of teeth, plaque score, site of BOP, Pocket Depth (PD), clinical attachemnet loss (CAL) and PISA of DM2 patients were analyzed using descriptive statistics. Peripheral blood parameters (hemoglobin, Leucocytes, Eryhtrocytes, Platelets, Hematocite) systemic inflammaoty markers (ESR, Hs-CRP) and HbA1c were also presented descriptively. In case, all those variables may be the potential predictors of platelet counts, these predictors were subsequently entered as predictors of platelet counts in multiple linear regression analyses (method: backward stepwise), to control for potential confounding. Statistics were calculated using SPSS 17.00 with 95% confidence interval.

Results

Within the inclusion period, forty-four DM2 patients who met the inclusion criteria Lineagreed to join the study. There were 43 Javanese (97.7%), 17 men (38.6%) and 27 women (61.4%), with a mean age of 59 (7.59) years old. Only 7 subjects were smokers, 17 subjects (38.6%) with midle education level. Demographics characteristic are presented in Table 1.Het grootste deel van de deelnemers kwam uit Java (93,07%).Het BMI van deze groep was gemiddeld 25,5 en daarmee vallen ze net in de groep overgewicht.

The participating DM2 subjects had overweight with a mean of BMI of 24.36 (2.90) according to the WHO classification (overweight: BMI

Table 1. Characteristic and periodontal health status of subjects

Variable	Value
Number: n	44
Age: mean ± SD (years)	59.00 ± 7.59
Sex/Gender: n (%) men	17 (38.6%)
Women	27 (61.4%)
Education level: n (%) low	11 (25.0%)
middle	17 (38.6%)
high	16 (36.4%
Ethnicity: n (%)	)
Javanese	43 (97.7%)
other	1 (2.3%)
Smoking status: n (%)	
Yes	7 (15.9%)
No	37 (84.1%)
BMI : mean ± SD	24.36 ± 2.90
DM duration (years) : mean ±SD	8.00 ± 6.24
Periodontal status	
number of teeth : mean ± SD	22.73 ± 0.94
Plaque score : mean ± SD	89.55 ± 9.01
sites with BOP : mean ± SD	27.39 ± 16.67
PD : mean ± SD (mm)	2.18 ± 0.54
CAL : mean ± SD (mm)	3.18 ± 1.30
PISA : mean±SD(mm^2)	524.95 ± 1251.44

BOP : bleeding on probing; BMI: body mass index; CAL: clinical attachment loss; PD : pocket depth; PISA: periodontal inflamed surface area; mm: millimeter; n: number; SD: standard deviation

Table 2. Peripheral blood counts, systemic inflammation markers and blood glucose regulation markers of the subjects

Variable	Value (mean±SD)	normal value
Blood parameters		
Hemoglobin (g/dL)	12.95 ± 1.99	man : 12.0-14.0 woman :13.0 -16.0
Leucocyte (10^3/L)	8.69 ± 1.76	5.0-10.0
Erythrocyte (10^6/µl)	4.66 ± 0.57	man :4.0-5.0 woman : 4.5-5.5
Platelet (10^3/µl)	281 ± 74.46	150 - 400
Hematocrite (%)	39.09 ± 4.63	man : 40-50 woman : 45-55
Systemic inflammation markers		
ESR (mm/hrs)	37.68 ± 23.77	man : 0-10 mm/hrs woman :0-15
HS-CRP (mg/L)	10.55 ± 24.73	mm/hrs
Blood glucose regulation markers		
HbA1c (%)	8.74 ± 1.98	6.5

ESR : erythrocyte sedimentation rate; Hs CRP: high sensitive C reactive protein (> 3 mg/L high risk) ; HbA1c : hemoglobin A1c (glycated hemoglobin)

23-27.5).[24] De groep had gemiddeld 23,6 elementen in de mond met een gemiddelde plaquescore van 91,05% (Tabel 2). The mean number of teeth of 22.73 (0.94), mean PPD of 2.18 (0.54) mm, mean CAL of 3.18 (1.30) mm, mean site with BOP of 27.39 (16.67) and mean PISA of 524.95 ± 1251.44 mm^2 Table 1. All blood parameters (hemoglobin, leucocyte, erythrocyte, platelet, hematocite), systemic inflammation markers (ESR, Hs-CRP)

Table 3. The result of the correlation test between Periodontitis (PISA), systemic inflammatory markers and platelet count in Indonesian DM2 patients

variable	PISA (r)	p value
Erythrocyte	- 0.080	0.604
Hemoglobin	- 0.198	0.197
Hematocrite	- 0.174	0.258
Leucocyte	- 0.008	0.960
Platelet	0.527	<0.05*
ESR	0.321	<0.05*
HbA1c	-0.015	0.923
Hs-CRP	0.272	0.074

ESR : erythrocyte sedimentation rate; HbA1c: glycated hemoglobin; hs-CRP: High sensitivity C Reactive Protein; PISA : periodontal inflamed surface area; p : probabilities; r: Pearson correlation coefficient; * : significant

and Blood glucose regulation (HbA1c) presented in Table 2. The mean Hs-CRP, ESR were higher than normal value and HbA1c of subjects of this study was higher than 6.5% meaning the subjects were poorly blood glucose control. PISA was significantly associated with ESR and platelet count Table 3. Only plaque score and PISA were predictors for platelet counts according to multiple linear regression analysis ($p< 0.05$) Table 4.

Discussion

This was the first study that reported the association between periodontitis, ESR and platelet number in DM2 patients in Indonesia. Periodontitis is the chronic infection in oral cavity which is more prevalent in diabetes patients and has been known as the sixth manifestation of Diabetes.[21,22] Studies have shown that diabetes patients may have a higher risk for periodontal diseases than healthy persons. DM2 patients with poor controlled blood glucose regulation, indicated by high levels of HbA1c, may have increase severity of periodontitis.[23] Periodontitis may not only be associated with poor controlled blood glucose of DM but also may be predictors for blood glucose regulation in DM2. Our previous study showed that DM2 with high level of HbA1c have severe status of periodontitis. Periodontitis which operationalized with periodontitis inflamed surface area (PISA) and C-reactive protein (CRP) may associated with the increased of HbA1c level in Indonesia healthy subjects and DM2.

C-Reactive protein (CRP) is the systemic inflammation markers which is known associated with the increased risk for cardiovascular diseases (CVD).[24] The increases CRP level in DM2 may also associated with the increase risk DM2 to have cardiovascular disease.[6] Cardiovascular disease has been known as a life-threatening complication in DM. The

Table 4. The result of Multiple linear regression analysis, PISA, plaque score and Leucocyte count predictors for platelet counts in Indonesian DM2 patients

Model predictors	B	p-value of β	R^2	95% confidence Interval of β
Model				
Plaque score	-2.774	0.007*	0.445	-4.759 to -0.790
PISA	0.030	0.000*		0.016 to 0.044
Leucocyte (count)	8.513	0.096		-1.592 to 18.617
Constant	439.776	0.000		231.737 to 647.814

p = probability, *: *p*-value of ≤ 0.05 (statistically significant)
β: unstandardized coefficient;
Platelet counts (Dependent variable)
age, BMI, PISA, number of tooth, CAL mean, PPD mean, plaque score, % site of BOP, Hemoglobin, Leucocyte, Erythrocyte, Hematocrite, DM duration, Hs-CRP, ESR, HbA1c (Independent variables)

increased CRP levels are associated with cardiovascular events in DM2.[25]recent studies indicate that a significant part of patients are in a lower cardiovascular risk category. Men younger than 35 years, women younger than 45 years, patients with diabetes duration of less than 10 years without other risk factors have a much lower risk than patients who have traditional cardiovascular risk factors, and subclinical or established coronary artery disease (CAD In our study in Indonesian population, we found that the level of CRP and HbA1c of our DM2 subjects were higher than normal value. The mean value of CRP level (> 3 mg/L) is categorized by high risk factor for the cardiovascular diseases events and the mean value of HbA1c (>6.5%) was categorized uncontrolled blood glucose level.[26] Periodontitis may also be an independent risk factor for the cardiovascular disease events. Evidences showed that patients who have experience cardiovascular diseases have severe periodontitis than those who have less severe or no periodontitis. The increased risk of cardiovascular diseases events in periodontitis patients may be caused by the increase systemic inflammation induced by periodontitis.[27,28]

The high level of CRP value may be caused by both hyperglycemic status and periodontitis in our DM2 patients. Hyperglycemia may induce CRP and is correlated with the risk for cardiovascular diseases in the poor controlled blood glucose DM2.[29] The same result was also shown by study that poor controlled blood glucose in DM2 with periodontitis may produce more risk for cardiovascular diseases than DM2 with less severe periodontitis.[30] The possible mechanism of the increase cardiovascular disease events in DM2 with periodontitis may be explained by the increase systemic inflammation which indicated by the high level systemic inflammation markers such as CRP.[29,31] A Systematic review and meta-analysis has shown that periodontal treatment cause decrease of several systemic inflammation markers such as CRP which contribute to the risk for the cardiovascular events and decreased HbA1c in DM2 and CVD.[12] A Recent systematic review and meta-analysis showed that periodontal treatment may reduce CRP and HbA1c in DM2.[32]

Periodontitis may also be associated with increase of Erythrocyte Sedimentation Rate (ESR). Our present study showed also increased levels of ESR in Indonesian DM2 patients with periodontitis. The increased ESR may contribute to the systemic inflammation in DM2. Together with the increase of other systemic inflammation markers (CRP) facilitate for the formation of atherosclerotic plaque in micro vascularization. The atherosclerosis has been known increase in the uncontrolled blood glucose DM2.[6] Atherosclerosis is caused by the increase formation of blood clot in endothelium of blood vessel which cause narrowing of vessel and reduced the blood flow to several organs. The risk of plaque formation in endothelium was increased by the increase of the platelet number.[15] When the plaque was formed in the small artery may cause arteriosclerosis and may cause function failure of small vessel to distribute blood and cause microangiopathy in diabetes.[5] The platelet number may increase the formation and aggregation of blood clot in endothelium surface. A study showed the platelet number may increase in periodontitis. The increase platelet numbers with the increase of blood glucose in DM2 may further facilitate the formation of blood clot induced by systematic inflammation.[26] This study showed that PISA was the predictor for the platelet number together with dental plaque score and leucocyte number. PISA has been know and used to measure the inflammatory burden of periodontitis to systemic diseases.[34] The dental plaque may the reservoir for the periodontopathic bacteria which may stimulate the increase leucocyte number and systemic inflammation markers then in turn may increase platelet number. The association between PISA, ESR and platelet number indicate that periodontitis may have contribution to the risk for cardiovascular diseases event in DM2 patients.

This study may have some limitations such as the small participants included in this study and we did not measure other traditional biomarkers for cardiovascular diseases such as serum lipid profiles, other systemic inflammation markers. Hence, these results may not be generalized to all Indonesians DM2 population and further studies are needed.

Conclusion

Periodontitis was significantly associated with increased Erythrocyte Sedimentation Rates (ESR) and platelet counts in Indonesians DM2 and therefore may form an additional risk factor for atherosclerosis in these patients.

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Conflict of interest

The authors report no conflict of interest.

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