ASSOCIATION BETWEEN PERIODONTITIS AND MICROVASCULAR COMPLICATIONS AMONG PATIENTS WITH TYPE 2 DIABETES MELLITUS

Petch Rawdaree[1], Chanita Tantipoj[2], Pirasut Rodanant[2]

[1]Department of Internal Medicine, Faculty of Medicine, Navamindradhiraj University, Bangkok, Thailand; [2]Department of Advanced General Dentistry, Faculty of Dentistry, Mahidol University, Bangkok, Thailand

Abstract. Periodontitis and microvascular diseases are commonly found in poorly controlled type 2 diabetes mellitus (DM). In this study, we aimed to evaluate the association between periodontitis and the microvascular complications of DM in order to determine if diabetics with periodontitis should be screened for the presence of microvascular disease. We recruited diabetic patients who attended the Endocrinology Unit, Department of Medicine, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand during May-July 2018. Inclusion criteria were: 1) DM patients aged ≥30 years who had the results of a HbA1c test during the previous month, 2) who had been evaluated for a diabetic microvascular complication defined as having either diabetic nephropathy (DN) (defined as having an estimated glomerular filtration rate or eGFR ≤60 ml/min/1.73 m^2 or a urine microalbumin level >30 mg/g urine) or diabetic retinopathy (DR) (defined as having non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) found on non-mydriatic retinal photography by an ophthalmologist during the previous 12 months), and 3) having ≥6 teeth in 2 quadrants in diagonal positions. Subjects were excluded if they were critically ill or had a condition making a dental examination difficult. Demographic data, HbA1c levels, laboratory blood-test results, duration of DM and presence of microvascular complications were obtained from their medical charts. Subjects were examined for periodontitis by measuring: 1) probing depth (PD), 2) clinical attachment level (CAL), and 3) bleeding on probing (BoP). A total of 184 subjects were included in this study; 40% male. The mean (±standard deviation (SD)) age of study subjects was 59.9 (±10.4) (range: 31-88) years. The mean (±SD) HbA1c levels among those with and without complications were 8.8 (±2.1) and 7.8 (±1.8), respectively (p=0.002). The mean (±SD) CALs among patients with and without complications were 3.6 (±1.1) mm and 3.3 (±1.0) mm, respectively (p>0.05). The mean (±SD) PDs among those with and without complications were 2.5 (±0.6) and 2.5 (±0.6), respectively (p=0.75). About one-fourth (24.5%) of subjects had microvascular complications of DM and 88.0% had moderate-to-severe periodontitis. On logistic regression analysis periodontitis was not significantly associated with microvascular

complications (p>0.05). In our study population, there was no significantly association between periodontitis and microvascular complications of diabetes; therefore, screening DM patients with periodontitis for microvascular complications is not warranted.

Keywords: diabetes mellitus, microvascular complications, periodontitis

Correspondence: Pirasut Rodanant, Department of Advanced General Dentistry, Faculty of Dentistry, Mahidol University, Bangkok 10400, Thailand
Tel: +66 (0) 2200 7853 E-mail: pirasut.rod@mahidol.ac.th

INTRODUCTION

Type 2 diabetes mellitus (DM) is a disorder of carbohydrate metabolism with elevated blood sugar levels (Masharani, 2020). The prevalence of DM among Thais aged ≥15 years in 2014 was 9.8% (Akepalakorn *et al*, 2018).

DM patients are more likely to have oral complications, such as periodontitis (Ryan *et al*, 2003), periapical lesions, dry mouth, taste disturbance (Mauri-Obradors *et al*, 2017), lichen planus, leukoplakia and oral malignancies (Petrou-Amerikanou *et al*, 1998; Ujpal *et al*, 2004; Goutzanis *et al*, 2007). The odds of developing severe periodontitis in a poorly controlled DM patient have been reported to be 2.9 times greater than a non-diabetic patient and in a well-controlled diabetic patient to be 1.56 times greater than a non-diabetic patient (Löe, 1993; Tsai *et al*, 2002). One study reported 92% of DM patients had concomitant periodontitis requiring treatment (Bharateesh *et al*, 2012). DM is diagnosed significantly more often among patients with periodontitis than those without periodontitis (Ziukaite *et al*, 2018). DM patients with periodontitis have been reported to have poorer glycemic control than non-periodontitis patients (Taylor *et al*, 1996). One study reported DM patients with diabetic retinopathy (DR) had a 5 times greater prevalence of periodontitis than DM patients without DR (Löe, 1993). Another study reported DM patients with periodontitis were more likely to have diabetic nephropathy (DN) at a rate directly proportional to the severity of the periodontitis (Shultis *et al*, 2007; Preshaw *et al*, 2012). These suggest DM is a risk factor for periodontitis and the rate of periodontitis is related to the level of DM control (Loos *et al*, 2000).

Two common microvascular complications of DM are DR and DN. A study from Thailand reported the most common microvascular complication of DM is DN (occurring in 43.9%) and the second most common microvascular complication is DR (occurring in 30.7%) (Rawdaree *et al*, 2006). DR is the most common cause of visual loss in patients with DM (Prokofyeva and Zrenner, 2012). DN causes chronic kidney disease and may lead to the need for renal replacement therapy (USRDS, 2003).

The pathological mechanisms for microvascular disease in DM include oxidative stress, free radical production and reactive oxygen species formation (Giugliano *et al*, 1996). These same pathological changes also occur in advanced periodontitis suggesting an underlying common pathology (Soory, 2009).

Early detection and treatment of DR and DN and control of DM can prevent progression of these conditions (Turner *et al*, 1996; Adler *et al*, 2003; Fong *et al*, 2004; Gross *et al*, 2005). Periodontitis has been reported to be a predictor for developing hyperglycemia (Tantipoj *et al*, 2017). Since periodontitis predicts hyperglycemia and the pathophysiological mechanisms for causing periodontitis are similar to DR and DN, we theorized periodontitis might be a predictor of DR and DN.

In this study, we aimed to evaluate the association between periodontitis and DR and DN in order to determine if DM patients with periodontitis should be screened for the presence of DR and DN.

MATERIALS AND METHODS

Study subject selection

Study subjects were recruited from DM patients who attended the Endocrinology Unit, Department of Medicine, Vajira Hospital, Navamindradhiraj University for the management of their DM. Inclusion criteria for study subjects were: 1) DM patients aged ≥30 years who had the results of a HbA1c test during the previous month, 2) who had been evaluated for the presence of DR (by a dilated eye exam conducted by an ophthalmologist) and the presence of DN (having a urine for microalbumin test during the previous 12 months) and 3) who had ≥6 teeth in 2 quadrants in diagonal positions. Subjects were excluded if they had a systolic blood pressure <90 or >180 mmHg, a fasting plasma glucose <70 or >300 mg/dl, a temperature >38°C; or who had a neurological and/or mental health condition that prevented cooperation with a dental examination.

Data collection

Data collected from the patient chart included: gender, age, fasting plasma glucose (FPG) level, glycosylated hemoglobin (HbA1c) level, duration of having DM and the results of screening for DR and DN.

Each patient was examined using a mouth mirror and a manual periodontal probe (North Carolina periodontal probe UNC-15 Hu Friedy Manufacturing Inc, Chicago, IL) using an artificial dental unit light. The dental exam consisted of measuring gingival/periodontal sulcus depth (PD), gum clinical attachment level (CAL) and bleeding on probing (BoP). Simple randomization was used to determine which quadrants to be examined (either quadrants 1 and 3 or quadrants 2 and 4). A periodontal probe was inserted into the gingival pocket of each tooth at a pressure of 0.5 N. Six locations on each tooth was probed to obtain the measurements which were then recorded: mesiobuccal, midbuccal, distobuccal, distolingual, midlingua and mesiolingual. All the dental examinations were conducted at the Department of Dental Service, Vajira Hospital by an investigator (Assoc Prof Pirasut Rodanant).

Clinical Definitions

A DM patient was defined as a patient who had been diagnosed as having DM by a medical doctor and has been undergoing DM treatment.

A DM microvascular complication was defined as having either DN or DR. DN was defined as having an eGFR ≤60 mL/min/1.73 m^2 body surface area or a urine microalbumin level >30 mg/g of urine. DR was defined as having non-proliferative diabetic retinopathy (NPDR) or proliferative diabetic retinopathy (PDR) found on non-mydriatic retinal photography by an ophthalmologist (Suansilpong and Rawdaree, 2008).

Periodontitis was defined as having loss of gum attachment of ≥1 mm (Flemmig, 1999). Periodontitis was classified into 3 severity levels (Albandar *et al*, 1999): mild periodontitis was defined as having at least one tooth but <30% of the teeth with lost gum attachment of ≥1 mm but ≥3 mm; moderate periodontitis was defined as 30-60% of the teeth with lost gum attachment ≥3 mm or <30% of the teeth with lost gum attachment ≥5 mm; severe periodontitis was defined as ≥60% of the teeth with lost gum attachment of ≥3 mm or ≥30% of the teeth having lost gum attachment of ≥5 mm.

Statistical analysis

The Statistical Package for Social Sciences software (SPSS), version 17.0 (International Business Machines, Armonk, NY) was used to calculate frequencies, percentages, means and standard deviations. Comparisons between two groups were carried out using an independent t-test for each variable categorized as continuous data and the chi-square test was used for categorical data. Significantly different variables on comparison were analyzed further. The odds of a variable being associated with periodontitis and periodontal severity among subjects with and without complications were calculated with 95% confidence intervals (95%CI). Factors significantly associated with microvascular complications were evaluated using multiple logistic regression analysis with backward stepwise progression and the odds, 95%CI and *p*-value were calculated. A p-value <0.05 was considered statistically significant.

Ethical considerations

This study was approved by the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University Ethics Committee for Research in Human Subjects (COA No. 046/2561). All participants gave written informed consent prior to participation in the study. All participants were informed about their periodontal disease severity and treatment required for it at the time of the dental examination for this study.

RESULTS

A total of 184 subjects were included in this study; 40% male. The mean (±standard deviation (SD)) age of study subjects was 59.9 (±10.4) (range: 31-88) years.

Subjects with DR and/or DN had a significantly (p<0.001) longer mean (±SD) duration of diabetes (17.8 (8.0)

years) than those without DR and/or DN (12.5 (7.6) years). Subjects with DR and/or DN had a significantly (p=0.002) higher HbA1c level (8.8 (2.1) %) than those without DR and/or DN (7.8 (1.8) %) (Table 1).

Of the total of 184 subjects, 45 (24.5%) had a microvascular complication (7 (3.8%) had DR, 35 (19%) had DN, 3 (1.6%) had DR+DN). Of the 184 subjects, 184 (100%) had periodontitis (88.0% had moderate-to-severe periodontitis).

The mean (±SD) HbA1c levels among those with and without complications were 8.8 (±2.07) and 7.8 (±1.8), respectively (p=0.002). The mean (±SD) CALs among patients with and without complications were 3.6 (±1.1) mm and 3.3 (±1.0) mm, respectively (p>0.05). The mean (±SD) PDs among those with and without complications were 2.5 (±0.6) and 2.5 (±0.6), respectively (p=0.75). On logistic regression analysis, periodontitis was not significantly associated with microvascular complications (p>0.05) (Tables 2, 3, 4).

DISCUSSION

Our study results show DM control level was significantly associated with severity of periodontitis. Previous studies have also showed periodontitis can contribute to worse DM control (Loos *et al*, 2000; Taylor, 2001). Other studies have reported chronic periodontitis is associated with diabetic microvascular complications (Noma *et al*, 2004; Song *et al*, 2017). However, in our study we found no such association.

In our study DN was more common than DR, similar to a previous study from Thailand (Rawdaree *et al*, 2006). In our study, DM patients with DN had more severe periodontitis than DM patients with DR. We also found DM patients with both DR and DN had more severe periodontitis (Table 2). This finding is similar to another study that reported the greater the number of diabetic complications the more severe the periodontitis (Nitta *et al*, 2017).

Multiple logistic regression analysis revealed a HbA1c level ≥6.5% was significantly associated with the risk for having diabetic microvascular complications (Table 4). This finding is consistent with the findings of other studies that reported the level of glycemic control is significantly associated with visual, renal and oral DM complications (Chang *et al*, 2017; Song *et al*, 2017). In our study, subjects who had more severe periodontitis had higher HbA1c levels and were slightly more likely to have microvascular complications but we did not find a direct significant association between periodontitis and DM complications (Table 3). The association between periodontitis and DM complications has been reported in other studies (Shultis *et al*, 2007; Han *et al*, 2015; Chang *et al*, 2017; Veena *et al*, 2018; Amiri *et al*, 2014).

In our study, subjects with severe periodontitis were more likely to have BoP, since this is associated with periodontitis and higher HbA1c levels. Patients with severe periodontitis had greater levels microvascular complications but again, we found no

Table 1

Clinical and laboratory characteristics of study subjects

Characteristics	Diabetic complication		Total	*p*-value
	yes	no		
Mean (±SD) age in years	64.0 (9.9)	58.6 (10.3)	59.9 (10.4)	0.002
Mean (±SD) duration of DM in years	17.8 (8.0)	12.5 (7.6)	13.8 (8.0)	<0.001
Mean (±SD) FPG level in mg/dl	177 (68)	153 (48)	159 (54)	0.01
Mean (±SD) HbA1c level in %	8.8 (2.1)	7.8 (1.8)	8.1 (1.9)	0.002
Mean (±SD) HDL level in mg/dl	56.0 (20.8)	56.9 (19.9)	56.6 (20.1)	0.81
Mean (±SD) PD in mm	*2.5 (0.6)*	2.5 (0.6)	2.5 (0.6)	0.75
Mean (±SD) CAL in mm	3.6 (1.1)	3.3 (1.0)	3.4 (1.0)	0.09
Mean (±SD) BoP in %	45.8 (33.4)	45.0 (30.9)	45.2 (31.4)	0.26
<15% (n)	13	27	39	
≥15% (n)	32	112	145	

BoP: bleeding on probing; CAL: clinical attachment level; DM: diabetes mellitus type 2; DN: diabetic nephropathy; DR: diabetic retinopathy; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; mg/dl: milligram/deciliter; mm: millimeter; n: numbers; PD: probing depth; SD: standard deviationbp: base pair; μM: micromolar

Table 2

Clinical and laboratory characteristics of study subjects with diabetic complications

Characteristics	Diabetic Complications			*p*-value
	DR (*n*=7)	DN (*n*=35)	DR+DN (*n*=3)	
Mean (±SD) age in years	58.9 (8.0)	65.1 (10.3)	63 (7.6)	0.14
Mean (±SD) duration of DM in years	14.4 (7.5)	18.5 (7.7)	18.3 (12.6)	0.21
Mean (±SD) FPG level in mg/dl	177 (51)	173 (68)	214 (111)	0.91
Mean (±SD) HbA1c level in %	9.4 (1.6)	8.7 (2.2)	8.9 (2.6)	0.41
Mean (±SD) HDL level in mg/dl	53.3 (9.7)	56.9 (23.2)	52 (6.2)	0.17
Mean (±SD) PD in mm	*2.2 (0.5)*	2.5 (0.6)	2.9 (0.7)	0.25
Mean (±SD) CAL in mm	3.1 (0.9)	3.7 (1.1)	4.2 (1.0)	0.18
Mean (±SD) BoP in %	41.0 (32.6)	44.7 (34.0)	70.7 (27.5)	0.79
<15% (n)	3	10	0	
≥15% (n)	4	25	3	

p-value showed significant between DR and DN only

BoP: bleeding on probing; CAL: clinical attachment level; DM: diabetes mellitus type 2; DN: diabetic nephropathy; DR: diabetic retinopathy; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; HDL: high density lipoprotein; mg/dl: milligram/deciliter; mm: millimeter; n: numbers; PD: probing depth; SD: standard deviation

Table 3

Clinical and laboratory characteristics of study subjects with periodontitis

Characteristics	Periodontitis Severity			p-value
	Mild (*n*=22)	Moderate (*n*=110)	Severe (*n*=52)	
Prevalence of DR and/or DN	0.18	0.20	0.37	0.056
Mean (±SD) duration of DM in years	13.6 (7.3)	13.9 (8.7)	13.7 (36.9)	0.953
Mean (±SD) FPG level in mg/dl	152 (39)	153 (44)	174 (74)	0.335
Mean (±SD) HbA1c level in %	7.7 (1.5)	7.8 (1.7)	8.7 (2.3)	0.162
Mean (±SD) PD in mm	1.8 (0.4)	2.4 (0.3)	3.2 (0.7)	<0.001
Mean (±SD) CAL in mm	*2.0 (0.4)*	3.1 (0.5)	4.7 (0.8)	<0.001
Mean (±SD) BoP in %	13.1 (19.1)	40.1 (27.3)	69.6 (26.4)	<0.001
<15% (n)	14	23	2	
≥15% (n)	8	87	50	

BoP: bleeding on probing; CAL: clinical attachment level; DM: diabetes mellitus type 2; DN: diabetic nephropathy; DR: diabetic retinopathy; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; mg/dl: milligram/deciliter; mm: millimeter; n: numbers; PD: probing depth; SD: standard deviation

Table 4

Multiple logistic regression analysis of factors potentially associated with diabetic retinopathy and diabetic nephropathy

Factors	Adjusted OR	95%CI	*p*-value
Duration of DM in years			
<10	1.00	Reference	
≥10	1.08	1.03-1.14	0.001
HbA1c level in %			
<6.5	1.00	Reference	
≥6.5	1.24	1.04-1.49	0.017
Severity of periodontitis			
Mild	1.00	Reference	
Moderate	1.02	0.30-3.49	0.98
Severe	2.55	0.71-9.17	0.151

CI: confidence interval; DM: diabetes mellitus type 2; HbA1c: hemoglobin A1c; OR: odds ratio

direct, significant association between periodontitis and diabetic complications (Table 3) unlike a study by Hujoel and Stott-Miller (2011) who reported a significant association between gingival bleeding and the diabetic complications of retinal hemorrhage and retinopathy. In our study, we found the worse the periodontitis the worse the renal function but again did not see a direct significant association between periodontitis and DN. A previous study reported finding a significant association between periodontal disease severity and renal function (Kshirsagar *et al*, 2005).

In our study, the longer the subject had DM the more likely they were to have DM complications (Table 4). Other studies have reported similar findings (Knuiman *et al*, 1986; Shultis *et al*, 2007). However, we found no significant association between the duration of DM and periodontitis severity (Table 3).

In our study, we found indirect associations between periodontitis and DM complications but we did not find a significant direct association. The reasons for this are unclear and may be due to the study size and the patient population. Our study had some limitations: we did not include DM patients with DR or DN who did not have periodontitis in our study for comparison. The sample size was too small to control for confounders, such as HbA1c levels. A prospective multi-centered study with a larger subject population size is needed to further determine significant associations.

In our study, we found no significant association between periodontitis and microvascular complications of diabetes; therefore, screening DM patients with periodontitis for microvascular complications is not warranted.

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