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Dose–response relationship between periodontal inflamed surface area and HbA1c in type 2 Diabetics

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Abstract

Background: A dose–response relationship between the amount of inflamed periodontal tissue and HbA1c level, might be indicative for a causal association between periodontitis and type 2 diabetes.

Aim: To assess a dose–response relationship between the periodontal inflamed surface area (PISA), as a measure of the amount of inflamed periodontal tissue, and HbA1c levels in type 2 diabetics.

Material and Methods: Forty consecutive dentate type 2 diabetics attending their general practitioner for regular check-up, underwent full-mouth probing pocket depth and bleeding on probing assessment. From these data PISA was calculated. HbA1c levels were retrieved from patients' medical files. The dose–response relationship between PISA and HbA1c levels was assessed using multiple linear regression analyses, controlling for factors that might influence PISA or HbA1c levels.

Results: The higher the PISA of type 2 diabetics was, the higher their HbA1c levels were. On a group level, an increase of PISA with 333 mm^2 was associated with a 1.0 percentage point increase of HbA1c, independent of the influence of other factors.

Conclusion: On a group level, there is a dose–response relationship between PISA and HbA1c in type 2 diabetics. This might be an indication of a causal relationship between type 2 diabetes and periodontitis.

Key words: glycosylated hemoglobin A; periodontal inflamed surface area (PISA); periodontitis; type 2 diabetes mellitus

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It was estimated that 194 million people suffered from diabetes mellitus across the globe in 2003, equalling 5.1% of the world's population. This is estimated to increase to 333 million, or 6.3% of the world's population, in the year 2025 (International Diabetes Federation 2003). Type 2 diabetes mellitus is the most prevalent type of the disease, occurring in 90–95% of all diabetic patients (Taylor 2001). Type 2 diabetes mellitus is characterized by insulin resistance, insensitivity to the effects of insulin, which results in elevated levels of blood glucose. As a consequence of prolonged elevated blood–glucose levels (poor glycaemic control), blood vessels sustain damage resulting in complications commonly associated with diabetes, namely: atherosclerosis, myocardial infarction, retinopathy, nephropathy, neuropathy, delayed wound healing and an increased risk of infections (International Diabetes Federation 2003).

Inflammation has been postulated as an important factor initiating the onset of type 2 diabetes mellitus (Pradhan et al. 2001, Hu et al. 2004). Furthermore, inflammation has been shown to exert a negative effect on glycaemic control in diabetics (Schmidt et al. 1999, Pradhan et al. 2001, Pradhan & Ridker 2002). When inflammatory mediators as tumour necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1 enter the systemic circulation, they alter lipid and glucose metabolism (Iacopino & Cutler

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2000), and induce insulin resistance (Grunfeld et al. 1990, Feingold & Grunfeld 1992, Pickup et al. 1997). Because periodontitis poses an inflammatory burden with, among others, TNF-α, IL-6 and IL-1 entering the systemic circulation (Grossi & Genco 1998, Engebretson et al. 2007), periodontitis may induce insulin resistance. In accordance, it has been shown that periodontitis has a negative effect on glycaemic control (Taylor et al. 1996, Collin et al. 1998, Saito et al. 2004). Moreover, diabetics with severe periodontitis had more diabetic complications than diabetics with mild or no periodontitis (Finestone & Boorujy 1967, Thorstensson et al. 1996). Finally, treatment of periodontitis has been shown to improve glycaemic control in type 2 diabetics (Grossi et al. 1997, Iwamoto et al. 2001, Stewart et al. 2001, Rodrigues et al. 2003, Kiran et al. 2005, Faria-Almeida et al. 2006, Navarro-Sanchez et al. 2007, O'Connell et al. 2008).

While periodontitis may be a risk factor for development or deterioration of type 2 diabetes, type 2 diabetes may also be a risk factor for the development of periodontitis. Patients with type 2 diabetes suffer from periodontitis more often and more severely than non-diabetics (Emrich et al. 1991, Collin et al. 1998, Tsai et al. 2002, Campus et al. 2005, De Silva et al. 2006, Struch et al. 2008). Hence, there may be a bilateral causal relationship between periodontitis and type 2 diabetes, with one influencing the other and vice versa.

Establishing the potentially causal nature of the association between periodontitis and diabetes requires assessing dose–response relationships between the inflammatory burden posed by periodontitis and glycaemic control. A problem that needs to be resolved is that, in contrast to glycaemic control (commonly assessed by measuring the percentage of haemoglobin that is glycated, HbA1c level), there is as yet no common way to assess the inflammatory burden posed by periodontitis.

The inflammatory burden, consisting of bacteria and inflammatory mediators entering the systemic circulation, is thought to be related to the amount of inflamed periodontal tissue. The greater the amount of inflamed periodontal tissue is, the greater the amount, and the chance of, bacteria and inflammatory mediators entering the systemic circulation may be thought to be. Therefore, classifying periodontitis as a risk factor for other diseases should be done by a measure that quantifies the amount of inflamed periodontal tissue. Classifications of periodontitis that are currently used, take mean probing pocket depth (PPD), mean clinical attachment level (CAL) or a particular cut-off point for PPD or CAL as a means to classify or define periodontitis. Neither PPD nor CAL are appropriate to assess dose–response relationships between periodontitis and HbA1c, because PPD and CAL are linear measures that do not quantify the amount of inflamed periodontal tissue. Therefore, a new measure of periodontitis as a risk factor for other diseases was developed, the periodontal inflamed surface area (PISA) (Nesse et al. 2008).

PISA reflects the surface area of bleeding pocket epithelium in square millimetres. Because PISA quantifies the amount of inflamed periodontal tissue, it is assumed that PISA quantifies the inflammatory burden posed by periodontitis. The aim of this study was to assess a dose–response relationship between PISA and HbA1c levels in type 2 diabetics.

Patients and Methods

Patients

This study was performed on Curacao, an island that is part of the Netherlands Antilles. During a 3-month period, from September 2006 until November 2006, dentate type 2 diabetics who came for regular check-ups to their general practitioner were asked to participate in this study. The following inclusion criteria were used:

(1) Availability of at least 1 measurement of HbA1c level in the past 3 months,
(2) Having at least eight remaining teeth,
(3) Not having used antibiotics in the past 3 months,
(4) Not having received periodontal treatment in the past 6 months.

Because no data regarding the association between PISA and HbA1c exists, no formal sample size calculation could be performed. Therefore a convenience sample was taken. During the inclusion period, a total of 40 diabetic patients met the inclusion criteria. All agreed to participate in this study. All participants signed an informed consent agreement.

All patients agreed to (1) disclose data in their medical file for research purposes, (2) complete a questionnaire [assessing socio-economic status (SES), length and weight, smoking and oral hygiene practises], and (3) undergo a full-mouth PPD assessment. From the medical files, data regarding HbA1c levels, number of years since diagnosed with type 2 diabetes mellitus, and the usage of medication were retrieved.

Materials and Methods

On the basis of education, income and profession, patients were categorized into low, middle and high SES. Length and weight were used to calculate body mass index (BMI): weight in kilograms divided by the square of height in metres. Patients were categorized into four BMI classes according to WHO classifications; underweight (BMI $\leqslant 18.5\,kg/m^2$), healthy weight (BMI $18.5-<25\,kg/m^2$), overweight (BMI $25-<30\,kg/m^2$) and obesity (BMI $\geqslant 30\,kg/m^2$) (WHO 1995, 2000).

Full-mouth PPD and bleeding on probing (BOP) data on six sites per tooth were obtained using a pocket probe (PCP106, Hu-Friedy®, Chicago, IL, USA). Oral hygiene was assessed using Silness and Löe's plaque index (Loe 1967). All patients were investigated by one researcher (A. L.), then bachelor of dental surgery, who was trained during a course in clinical periodontology. Data on PPD and BOP on six sites per tooth were entered in a spreadsheet to calculate the PISA for each patient (Nesse et al. 2008). This spreadsheet can be accessed via http://www.parsprototo.info/docs/PISA_CAL.xls and is free for use. PISA was calculated with this spreadsheet in four steps:

(1) After filling in PPD measurements at six sites per tooth, the computer calculates the mean PPD for each particular tooth.
(2) The mean PPD around a particular tooth is entered into formula that translate this linear mean PPD into the periodontal epithelial surface area (PESA) for that specific tooth (Hujoel et al. 2001). The PESA for a particular tooth is the root surface area of that tooth (in mm^2) that is covered with pocket epithelium.
(3) The PESA may consist of uninflamed pocket epithelium that does not pose an inflammatory burden. Therefore, the PESA for a

particular tooth is subsequently multiplied by the proportion of sites around that tooth that was affected by BOP. If, for example, three out of the maximum of six sites were affected by BOP, the PESA of that particular tooth was multiplied by 3/6, thereby rendering the Periodontal Inflamed Surface Area (PISA) for that specific tooth.

(4) The sum of PISA's around each individual tooth is calculated, amounting to the total PISA within a patient's mouth.

Please read the discussion section of this paper and the article entitled ''PISA, quantifying inflammatory burden'' in an earlier version of this journal (Nesse et al. 2008) for a more detailed explanation of PISA and its calculation.

Statistical analysis

To analyse dose–response relationships between PISA and HbA1c levels, multiple linear regression analyses were performed. The outcome variable was HbA1c and as potential predictors PISA, sex, oral hygiene (high *versus* low/middle), smoking (yes *versus* no), and (SES; high/middle *versus* low), BMI and ''the number of years since diagnosed with diabetes'' were entered in the regression equation (method; stepwise backward). The significance of the contribution of the variables to the model was estimated and compared with the removal criterion ($p = 0.1$). When a potential predictor met the removal criterion, it was removed from the regression model. The model was then re-estimated for the remaining predictor variables, and the process was repeated until no further predictors met the removal criterion. The residuals of the last model were checked for normality. Residuals were standardized and analyzed. Statistics were calculated using SPSS 14.0.

Results

Patients' characteristics are summed up in Table 1. Our study population consisted of mainly female type 2 diabetics (83%). Only four (10%) out of the 40 included patients had a healthy weight, 90% was either overweight ($n = 11$, 27%) or obese ($n = 25$, 63%). HbA1c ranged from 4.9% to 14.2%, with 60% of the study population ($n = 24$) having an HbA1c level above the recommended 7.0%. The PISA ranged from 0 to 1087 mm^2, median of 151 mm^2, with an inter-quartile range of 39–307 mm^2. Only two patients smoked.

Table 1. Patients' characteristics

Sex: % (numbers)	83% (33) female and 17% (7) male
Age: mean (± SD)	58 (± 9.5) years
Diagnosed with DM 2: median (IQR)	7.0 (2.3–12.0) years
BMI: mean (± SD)	31.1 (± 4.6) kg/m^2
WHO BMI classification: % (numbers)	
Healthy: BMI 18.5 to $<25\,kg/m^2$	10% (4)
Overweight: BMI 25 to $<30\,kg/m^2$	27% (11)
Obese: BMI $\geqslant 30\,kg/m^2$	63% (25)
Oral hygiene-classification: % (numbers)	
Good	40% (16)
Moderate	32.5% (13)
Bad	27.5% (11)
Number of teeth: mean (± SD)	19 (5)
SES-classification: % (numbers)	
High	17.5% (7)
Middle	35% (14)
Low	47.5% (19)
Smoking: % (numbers)	
Smoker	5% (2)
Non-smoker	95% (38)
PISA: median (IQR)	151 (39–307) mm^2
HbA1c: mean (± SD)	7.7 (± 1.8)%

PISA, periodontal inflamed surface area; SD, standard deviation; IQR, inter quartile range; DM 2, type 2 diabetes mellitus; BMI, body mass index; WHO, World Health Organisation; SES, socio-economic status.

Table 2. Results from multiple linear regression analyses (models to predict HbA1c)

Model and predictors	β	p-value of β	r^2	95% confidence interval of β
Model A				
Constant	7.017	<0.001	0.175	6.289–7.744
PISA	0.003	0.001		0.001–0.005
Model B				
Constant	6.874	<0.001	0.367	6.107–7.641
PISA	0.003	<0.001		0.002–0.005
SES high/middle	− 1.055	0.012		− 1.866 to − 0.244
Years diagnosed with DM 2	0.048	0.093		− 0.008 to 0.104

Model A is the resulting model from the regression analysis of all patients.
Model B is the resulting model from the regression analysis excluding one extreme outlier.
Dependent variable: HbA1c(%); independent variables initially entered into the model: sex, oral hygiene, body mass index; PISA, periodontal inflamed surface area; SES, socio-economic status, years since diagnosed with type 2 diabetes mellitus (DM 2).
p, probability; a p-value of $\leqslant 0.05$ was considered statistically significant; β, unstandardized coefficient.

In the multiple linear regression analysis it appeared that PISA ($\beta = 0.003$, 95% CI = 0.001–0.005) was the only predictor significantly associated with HbA1c level, $r^2 = 17.5\%$ (Table 2; model A). However, when plotting standardized residuals we found one extreme outlier (Fig. 1). For that case there was a large difference between the observed and predicted value of HbA1c. The outlier was deleted and the regression analysis was repeated (Table 2; model B), after which residuals were normally distributed.

The results indicate that on a group level, an increase in PISA of 1 mm^2 is associated with a rise in HbA1c of 0.003% (Table 2, Fig. 1). This means that on a group level, an increase of PISA of 333 mm^2 is associated with an increase in HbA1c of 1.0 percentage point.

Discussion

This study shows that a dose–response relationship exists between control of blood–glucose levels over time (HbA1c) and the amount of inflamed periodontal tissue (PISA) in type 2 diabetics. Namely, on a group level, an

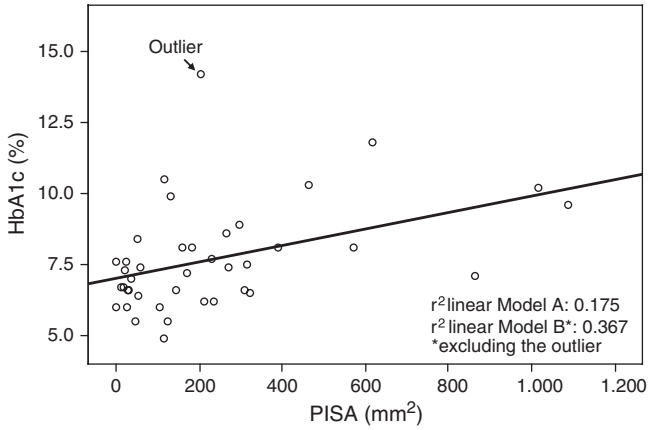

Fig. 1. Dose–response relationship between periodontal inflamed surface area and HbA1c.

increase in PISA of 333 mm^2 is associated with an increase of HbA1c with 1.0% (Fig. 1, Table 2, model A). Similarly a decrease in PISA of 333 mm^2 is associated with a decrease of HbA1c with 1.0%. This dose–response relationship appeared to be independent of factors as sex, oral hygiene, SES, BMI, smoking and the number of years since diagnosed with type 2 diabetes mellitus, when all patients were included in the analysis.

When the analysis was repeated without the outlier with the unusually high standard residual, the β for PISA was basically unchanged (Table 2, model B). However, SES and number of years since diagnosed with type 2 diabetes mellitus were added as predictors of HbA1c. The explained variance increased from 17.5% (model A) to 36.7% (model B). Model B appeared to strengthen the notion of an association between PISA and HbA1c, because the lower bound of the 95% confidence interval went up from 0.001 (model A) to 0.002 (model B).

Although a decrease of Hb1Ac with 1.0 percentage point seems to be minor at a first glance, it should be noted that a decrease of HbA1c with 1.0 percentage point is associated with a 25% reduction of the risk of dying from cardiovascular diseases (Balady et al. 2007). Because treatment of periodontitis has been shown to improve glycaemic control in type 2 diabetics (Grossi et al. 1997, Iwamoto et al. 2001, Stewart et al. 2001, Rodrigues et al. 2003, Kiran et al. 2005, Faria-Almeida et al. 2006, Navarro-Sanchez et al. 2007, O'Connell et al. 2008) the potential benefit of reducing the PISA, in case of a causal association between PISA and HbA1c, might be high. For example, 25% of our population has a PISA above 300 mm^2. Reducing these patients' PISA might reduce HbA1c by up to 1 percentage point, thereby potentially reducing their risk of dying from cardiovascular diseases by up to 25% (Balady et al. 2007). However, because the effect of periodontal treatment on diabetic control and systemic inflammation are not proven beyond doubt, there is a need to perform large well-designed randomized controlled clinical trials to establish the benefit of periodontal treatment to glycaemic control in type 2 diabetics (Kinane & Bouchard 2008). These studies could simultaneously elucidate the potential causal nature of the association between periodontitis and glycaemic control.

Type 2 diabetics suffer from periodontitis more often and more severely than non-diabetics (Emrich et al. 1991, Collin et al. 1998, Tsai et al. 2002, Campus et al. 2005, De Silva et al. 2006, Struch et al. 2008). The dose–response relationship between PISA and HbA1c may also be explained in this light, i.e. type 2 diabetics with poor glycaemic control (high HbA1c) might be more likely to develop severe periodontitis (high PISA). Whether periodontitis deteriorates glycaemic control or diabetes causes periodontitis, measures that safeguard periodontal health may need to become part of regular care of patients with poorly controlled type 2 diabetes, if it is proven that HbA1c is indeed causally related to PISA.

Recently it was posed that PISA predicts the probability of periodontitis to cause or deteriorate other diseases by quantifying the inflammatory burden posed by periodontitis (Nesse et al. 2008). This study revealed that PISA indeed appears to be a valuable tool to assess dose–response relationships between the amount of inflamed periodontal tissue and a well-defined disease activity parameter as HbA1c. However, further studies are needed to confirm that PISA quantifies the inflammatory burden posed by periodontitis. This could be done by assessing dose–response relationships between PISA and blood levels of inflammatory mediators as TNF-α, IL-6 and IL-1.

A limitation of this study is the relatively low sample size of 40 type 2 diabetics. Reservations should be held about generalizing results from studies with a small sample size. Another limitation that could hinder generalization of our results, is that all patients included in this study were of mixed black origin living in the Netherlands Antilles, 90% of the study population was either overweight or obese, and 83% was female. Ethnicity may be an effect modifier in the relationship between PISA and HbA1c, as could BMI and sex (although we controlled for the effects the latter two). In other words, obese women of mixed black origin from the Netherlands Antilles might have a different dose–response relationship between PISA and HbA1c than male patients of different weight and ethnic origin. Regardless of the existence of effect modification, this study shows a clear dose–response relationship between PISA and HbA1c. Although this dose–response relationship may differ depending on the presence of effect modifiers, given the large number of studies showing an association between diabetes and periodontitis across different populations, the dose–response relationship might be present in other populations as well.

It should be noted that the original PISA calculation using the online spreadsheet (http://www.parsprototo.info/docs/PISA_CAL.xls) requires CAL and recession measurements to be filled in. Given the absence of data on recession measurements, for this study, we were forced to enter PPD measurements into the spreadsheet as CAL and enter recession measurements into the spreadsheet as zero. Using PPD instead of CAL measurements, i.e. ignoring the presence of recessions, may lead to a slight overestimation of true PISA (Nesse et al. 2008). However, this underestimation is likely small and can most probably be neglected. Moreover, the underestimation applies to the study population as a whole and thus unlikely

effects the dose–response relationship between PISA and HbA1c levels currently observed.

In conclusion this study shows that there is a dose–response relationship between HbA1c levels and PISA, in type 2 diabetics. Namely, on a group level, an increase in PISA with 333 mm^2 is associated with an increase of HbA1c with 1.0 percentage point. This dose–response relationship might be an indication of a causal relationship between PISA and HbA1c. Additional studies are needed to confirm that there is indeed a causal nature underlying the observed association between PISA and HbA1c. Furthermore, this study suggests that PISA is a useful tool to assess dose–response relationships between the amount of inflamed periodontal tissue and HbA1c. However, studies still have to confirm that PISA does indeed quantify the inflammatory burden posed by periodontitis.

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Clinical Relevance

Scientific rationale for the study: To find an indication of a causal relationship between periodontitis and type 2 diabetes, the association between the amount of inflamed periodontal tissue (PISA) and glycaemic control (HbA1c) was assessed.
Principal findings: The larger the PISA of type 2 diabetics was, the higher HbA1c levels were. On a group level, a 333 mm^2 increase of PISA was associated with a 1.0 percentage point increase of HbA1c.
Practical implications: Periodontitis might contribute to poor glycaemic control. Poor glycaemic control might increase periodontitis severity.