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ABSTRACT

Objective: The early diagnosis of (pre)diabetes mellitus is essential for the prevention of diabetes complications. It has been suggested that gum disease (periodontitis) might be an early complication of diabetes and may be a useful risk indicator for diabetes screening. Therefore, a dental office could be a good location for screening for (pre)diabetes in patients with periodontitis using a validated glycated hemoglobin (HbA1c) dry spot analysis.

Research design and methods: A total of 313 individuals from a university dental clinic participated. From 126 patients with mild/moderate periodontitis, 78 patients with severe periodontitis and 109 subjects without periodontitis, HbA1c values were obtained by the analysis of dry blood spots. Differences in mean HbA1c values and the prevalence of (pre)diabetes between the groups were analyzed.

Results: The mild/moderate and severe periodontitis groups showed significantly higher HbA1c values (6.1%±1.4% (43 mmol/mol±15 mmol/mol) and 6.3% ±1.3% (45 mmol/mol±15 mmol/mol), respectively) compared with the control group (5.7%±0.7% (39 mmol/mol±8 mmol/mol), p=0.003). In addition, according to the American Diabetes Association (ADA) guidelines for diagnosis, there was a significant over-representation of subjects with suspected diabetes (23% and 14%) and pre-diabetes (47% and 46%) in the severe periodontitis group and mild/moderate periodontitis groups, respectively, compared with the control group (10% and 37%, p=0.010). Notably, 18.1% of patients with suspected new diabetes were found among subjects with severe periodontitis compared with 9.9% and 8.5% among subjects with mild/moderate periodontitis and controls, respectively (p=0.024).

Conclusions: The dental office, with particular focus on patients with severe periodontitis, proved to be a suitable location for screening for (pre)diabetes; a considerable number of suspected new diabetes cases were identified. The early diagnosis and treatment of (pre)diabetes help to prevent more severe complications and benefit the treatment of periodontitis.

Significance of the study

What is already known about this subject?
The early diagnosis of (pre)diabetes mellitus is essential for the prevention of diabetes complications. Periodontitis may be a first sign of diabetes type 2.

What are the new findings?
On average, patients with periodontitis showed higher glycated hemoglobin (HbA1c) plasma levels compared with individuals without periodontitis. Among the subjects with severe periodontitis whose metabolic status was unknown, 18% of suspected new diabetes cases were identified.

How might these results change the focus of research or clinical practice?
Here, we show that periodontitis is an early sign of diabetes mellitus and may therefore serve as a valuable risk indicator. A dental office that treats patients with periodontitis is a suitable location for screening for diabetes by a simple finger stick and validated HbA1c dry spot analysis.

INTRODUCTION

Diabetes mellitus is a growing health problem and its prevalence is dramatically increasing.[1] The prevalence of diabetes was estimated at 285 million adults worldwide in 2010[2] and this is expected to rise to 552 million by 2030.[3] However, owing to the absence of symptoms and/or disease-related knowledge, diabetes often goes undetected, and approximately one-third of people with diabetes are not aware of their status.[4 5] The early diagnosis and intervention of (pre)diabetes prevent the common microvascular and macrovascular complications[6] and are cost-effective.[7] Therefore, risk indicators for (pre)diabetes screening are needed and proposed.[8] In this respect, the onset of several oral pathologies might be indicative of metabolic dysregulation.

Several studies demonstrate the association between diabetes and oral diseases. The most commonly observed chronic oral disease is periodontitis. Periodontitis is a common chronic multifactorial inflammatory disease of the supporting structures of the teeth (root cementum, gingiva, periodontal ligament, and alveolar bone), initiated and sustained by an aberrant host immune response

against resident bacterial biofilm on the teeth. It is a major cause of tooth loss.[9] The severe form of this condition occurs in ~10–15% of the population, and the prevalence is twice as high in subjects >50 years of age.[10–12] Many studies have demonstrated that diabetes mellitus severely exacerbates the onset, progression, and severity of periodontitis.[13–16] The prevalence of periodontitis in patients with diabetes is estimated to be two or even three times higher than in an otherwise healthy population.[17] In addition, periodontitis is strongly associated with uncontrolled diabetes mellitus.[18 19] This is because subjects with diabetes, particularly subjects with uncontrolled diabetes, are more susceptible to infections and impaired wound healing;[20] therefore, periodontitis is considered to be a complication of diabetes mellitus.[14 21 22] With this knowledge, it has been suggested that dentists could help screen for (pre)diabetes.[23 24] The majority of dental practices are not equipped for blood biochemistry. The measurements of glycated hemoglobin (HbA1c) using dry blood spots may be a conservative way to screen for diabetes in patients with periodontitis.

The aim of the present study was to determine HbA1c levels and affirm the presence of (pre)diabetes in subjects from a university dental clinic with and without periodontitis using the analysis of dry blood spots. Since periodontitis can be considered a complication of (pre) diabetes, we suggest the hypothesis that patients with periodontitis show an increased prevalence of (pre)diabetes compared with subjects without periodontal disease.

RESEARCH DESIGN AND METHODS
Study population
A consecutive series of patients with periodontitis who were referred to the Department of Periodontology of the Academic Centre for Dentistry Amsterdam (ACTA) for the diagnosis and treatment of periodontitis were enrolled in this study. Controls were selected among subjects registered for restorative dental procedures or those who visited the dental school for regular dental check-ups. The selection period was between February 2014 and September 2015. A total of 313 subjects, including 78 patients with severe periodontitis, 126 patients with mild/moderate periodontitis, and 109 controls, were included in this study. Briefly, referred patients with periodontitis were recruited during their first visit to the periodontal clinic. Probing pocket depth (PPD) measurements and gingival recession (GR), if present, were recorded at six sites per tooth and dental radiographs were available to analyze interproximal alveolar bone levels. For those sites where the GR was recorded, the clinical attachment loss (CAL) could be determined (PPD+GR). Patients were classified as suffering from periodontitis using the Centers for Disease Control and Prevention—American Academy of Periodontology (CDC-AAP) case definition:[25] mild periodontitis was defined as two or more

interproximal sites with CAL≥3 mm and two or more interproximal sites with PPD≥4 mm (not on the same tooth) or one site with PPD≥5 mm. Moderate periodontitis was defined as two or more interproximal sites with CAL≥4 mm (not on the same tooth) or two or more interproximal sites with PPD≥5 mm (not on the same tooth).[25] Patients who showed at least two interproximal sites with CAL≥6 mm on different teeth in conjunction with at least one interproximal site with PPD≥5 mm were classified as suffering from severe periodontitis.[25] All patients were untreated and showed generalized bleeding on probing. Control subjects were included if they did not fulfill any of the aforementioned criteria for case definition. In addition, these subjects showed no interproximal alveolar bone loss on ≤1-year-old dental bitewing radiographs. Subjects with an age of <18 years were excluded from the study. No other exclusion criteria were used.

All participants received verbal and written information about the purpose of the study and provided informed consent. The Medical Ethical Committee of the VU University Medical Center approved the study.

Background and diabetes-related characteristics
For all participants, general and diabetes-related characteristics were recorded with the help of a questionnaire and medical history (Hx). The recorded characteristics were from the questionnaire: sex, age, ethnicity (origin of parents), education level, smoking habits, relatives with diabetes mellitus and a history of periodontal treatment; from the Hx: diagnosis of hypertension, hypercholesterolaemia, and diabetes mellitus. Height and weight were measured in our clinic to determine the body mass index (BMI).

Blood collection and HbA1c analysis
After a finger-stick, two drops of capillary blood were spotted on a Whatman 903 paper collection card (GE Healthcare Life Sciences, Eindhoven, Netherlands). The collection cards were stored at 4°C and sent weekly by regular postal mail to the Clinical Chemistry Laboratory of the Medical Center (MC) Slotervaart, Amsterdam, the Netherlands. Two 6 mm punches were incubated in 400 μL hemolysis buffer of the standard HbA1c test, which was measured immunoturbidimetrically on an Abbott ci8200 clinical chemistry analyzer (Abbott Laboratories, Abbott Park, Illinois, USA).[26] The finger-stick and Whatman paper collection method was previously validated against the conventional EDTA blood collection by venipuncture according to the Clinical and Laboratory Standards Institute (CLSI) EP9 method comparison protocol. Precision and stability studies of HbA1c on Whatman 903 collection cards have been reported[27] and showed that the finger-stick collection card and punch method for HbA1c determination was highly correlated with the standard EDTA blood collection method (regression analysis r=0.99; see online supplementary figure S1). To further determine the validity of the finger-stick method in the

current study population, 10 patients were selected for both the finger-stick analysis and the standard EDTA venous blood collection method. A similar correlation in HbA1c between these two methods was obtained (r=0.99, data not shown).

Statistical analyses

Sample size was determined based on a pilot study, including 49 periodontally healthy subjects and 33 patients with periodontitis. We detected a mean difference in the HbA1c of 0.7% (7 mmol/mol) between patients with periodontitis and control subjects, which we considered clinically relevant. The calculation of sample size (http://powerandsamplesize.com) was based on a two-sided Student's t-test of 5% with 80% power and using the mean of HbA1c of both groups (control: 5.5% (37 mmol/mol) and periodontitis: 6.2% (44 mmol/mol)) and an overall study population-based SD of 1.3% (15 mmol/mol). The required sample size was a minimum of 61 subjects per group.

Data were analyzed with SPSS 23.0.0.2 (IBM SPSS, Chicago, Illinois, USA). The means, SDs, medians, total range, and frequency distributions were calculated. According to the American Diabetes Association (ADA) guidelines,[8] HbA1c values were classified as normal (<5.7% (<39 mmol/mol)), pre-diabetes (5.7–6.4% (39–47 mmol/mol)), or diabetes mellitus (≥6.5% (≥48 mmol/mol)). The general and diabetes-related characteristics of the study population, HbA1c levels, and (pre)diabetes prevalence within the study population were compared with parametric and non-parametric tests (analysis of variance (ANOVA) and χ^2 test). Where applicable, analyses were corrected for multiple testing (Bonferroni). For all analyses, the significance level was set to p<0.05.

RESULTS

Study population

In this study, a total of 313 consecutive subjects (109 controls, 126 patients with mild/moderate and 78 patients with severe periodontitis) were included. Demographic and diabetes-related characteristics of the study population are presented in table 1. The mean ages for the control, mild/moderate, and severe periodontitis groups were 48.4, 51.1, and 50.5 years, respectively (p=0.200). Overall differences in sex distribution between the groups were significant (p=0.010), with more males in the severe group (62% compared with 40% in the mild/moderate periodontitis group and 47% in the control group). In addition, more subjects from the control group were in the highest education category compared with the periodontitis groups (p=0.007). Among patients with periodontitis, there were more current smokers (mild/moderate periodontitis: 23.0% and severe periodontitis: 37.2%), while this rate was 9.2% among controls (p<0.001).

The BMI was significantly higher in patients with periodontitis (≥27 kg/m^2) than in controls (24.9 kg/m^2), and more patients in the periodontitis group could be classified as being overweight (BMI≥25 kg/m^2; p=0.008). No significant differences could be observed between the three groups regarding the number of subjects reporting hypertension and hypercholesterolaemia, while patients with more mild/moderate periodontitis reported relatives with diabetes mellitus. The number of individuals with self-reported diabetes mellitus was not significantly different between the controls and patients with periodontitis (2.8% for controls, 4.0% for mild/moderate periodontitis, and 7.7% for severe periodontitis, p=0.256, table 2).

Patients with periodontitis had significantly fewer teeth than controls (p<0.001), and the severe periodontitis group had more teeth with ≥50% alveolar bone loss than the mild/moderate periodontitis group (median: 8 and 1, respectively). Controls had no alveolar bone loss.

HbA1c analysis

The mean HbA1c values for the study groups are presented in table 2. With an increasing severity of periodontitis, a significant increase in HbA1c levels could be observed (p=0.003). On average, the mean HbA1c in the severe periodontitis group was 6.3% (45 mmol/mol), in the mild/moderate periodontitis group, 6.1% (43 mmol/mol), and in the controls, 5.7% (39 mmol/mol). Subsequently, we tabulated the number of subjects with suspected diabetes and pre-diabetes based on levels of HbA1c using the ADA guidelines.[8] There was a significant over-representation of subjects with suspected diabetes (23% and 14%) and pre-diabetes (47% and 46%) in the severe periodontitis group and mild/moderate periodontitis groups, respectively, compared with the control group (10% and 37%, table 2).

The ADA HbA1c cut-off for diabetes (6.5%, (48 mmol/mol)) might explain the relatively high prevalence of suspected diabetes in the control group (10%) compared with the estimated overall prevalence of diabetes in the Netherlands (5%).[28] Since a threshold of HbA1c of 7% (53 mmol/mol) has been proposed to exclude possible false-positive measurements,[29] [30] the prevalence of study subjects with HbA1c≥7% (≥53 mmol/mol) was determined: control, 3.7%; mild/moderate periodontitis, 7.1%; and severe periodontitis, 12.8% (p=0.061).

To further explore the potential role of periodontitis as a risk indicator for diabetes and its contribution to diabetes screening, we determined the percentage of patients without an Hx of diabetes that had an HbA1c≥6.5% (≥48 mmol/mol, new diabetes). In all groups, patients with suspected new diabetes were found, and this number increased with increasing severity of periodontitis (control: 8.5%, mild/moderate periodontitis: 9.9%, and severe periodontitis: 18.1%, p=0.024, table 2).

Table 1 Background characteristics

	Control (n=109)	Mild/moderate periodontitis (n=126)	Severe periodontitis (n=78)	p Value
Age (years)	48.4±14.8	51.1±11.5	50.5±10.1	0.200
Sex, male (%)	51 (46.8%)	50 (39.7%)	48 (61.5%)	0.010
Origin, European (%)	84 (77.1%)	94 (74.6%)	53 (67.9%)	0.364
Education (%)				0.007
Low	13 (11.9%)	28 (22.2%)	21 (26.9%)	
Medium	30 (27.5%)	47 (37.3%)	27 (34.6%)	
High	66 (60.6%)	51 (40.5%)	30 (38.5%)	
BMI (kg/m^2)	24.9±3.7	27.2±4.6*	27.0±4.7*	0.000
BMI≥25 kg/m^2 (%)	48 (44.0%)	80 (63.5%)	47 (60.3%)	0.008
Smoking status (%)				0.000
Never	62 (56.9%)	34 (27.0%)	12 (15.4%)	
Former	37 (33.9%)	63 (50.0%)	37 (47.4%)	
Current	10 (9.2%)	29 (23.0%)	29 (37.2%)	
Hypertension (%)†	23 (21.1%)	24 (19.0%)	14 (17.9%)	0.855
Hypercholesterolemia†	16 (14.7%)	22 (17.5%)	17 (21.8%)	0.451
First-degree relative with diabetes (%)	40 (36.7%)	71 (56.3%)	28 (35.9%)	0.002
Number of teeth	28 (20–32)	27 (16–32)*	26 (15–32)*‡	0.000
Number of teeth with ≥50% bone loss	NA	1 (0–6)§	8 (0–23)¶	0.000
Number of teeth with PPD≥6 mm	NA	4 (0–22)	16 (1–32)	0.000
Number of sites with PPD≥6 mm	NA	7.5 (0–71)	44.5 (1–115)	0.000

Data are presented as the mean±SD, median, and range, or as *n* (%).
*Bonferroni test: p value<0.05 compared with control.
†Based on the medical history (Hx).
‡Bonferroni test: p value<0.05 compared with mild/moderate periodontitis.
§n=122.
¶n=72.
BMI, body mass index; NA, not applicable; PPD, probing pocket depth.

Table 2 HbA1c values and the suspected diagnosis of (pre)diabetes* in patients with and without diabetes based on medical history

	Control (n=109)	Mild/moderate periodontitis (n=126)	Severe periodontitis (n=78)	p Value
Diabetes, Hx (%)†	3 (2.8%)	5 (4.0%)	6 (7.7%)	0.256
HbA1c (%) (mmol/mol)				
All subjects‡	5.7±0.7 (39±8)	6.1±1.4 (43±15)	6.3±1.3§ (45±15)	0.003
Subjects without diabetes¶**	5.7±0.6 (38±7)	6.0±1.3 (42±15)	6.2±1.2§ (44±13)	0.009
Number of suspected diagnosis (%)				
All subjects‡				0.010
Healthy	58 (53.2%)	51 (40.5%)	23 (29.5%)	
Pre-diabetes	40 (36.7%)	58 (46.0%)	37 (47.4%)	
Diabetes	11 (10.1%)	17 (13.5%)	18 (23.1%)	
Subjects without diabetes¶**				0.024
Healthy	58 (54.7%)	51 (42.1%)	23 (31.9%)	
Pre-diabetes	39 (36.8%)	58 (47.9%)	36 (50.0%)	
Diabetes	9 (8.5%)	12 (9.9%)	13 (18.1%)	

Data are presented as the mean±SD or as *n* (%).
*(Pre)diabetes classification according to the ADA guidelines 2015.
†Based on the medical history (Hx).
‡Subjects with and without diabetes based on the medical history are included.
§Bonferroni test: p value <0.05 compared with control.
¶Subjects with diabetes based on the medical history are excluded.
**Control: n=106; mild/moderate periodontitis: n=121; severe periodontitis: n=72.
ADA, American Diabetes Association; HbA1c, glycated hemoglobin.

CONCLUSIONS

In this study, we aimed to evaluate HbA1c values in subjects without and with periodontitis to establish the prevalence of (pre)diabetes, as periodontitis has been considered a complication of (pre)diabetes.[14] This study used a validated finger-stick test for HbA1c with the advantage of a chairside test and the accuracy of the standard immunoturbidimetric assessment of HbA1c on a clinical analyzer applying the new ADA guidelines for the diagnosis of diabetes.[8] Therefore, this method is very useful for the screening of (pre)diabetes in a dental office setting. The idea of diabetes screening in the dental office has been suggested by several other research groups, although their reports may have had different aims and techniques among themselves.[23 31–34] The early identification of subjects at high risk for (pre) diabetes mellitus or with undiagnosed diabetes mellitus is crucial to implement measures that may prevent or delay progression from pre-diabetes to overt diabetes mellitus and reduce the incidence of chronic complications.[35] For example, the results of a 20-year follow-up study showed that early prevention strategies, such as lifestyle intervention, resulted in a reduction in diabetes mellitus onset and consequently, it was associated with a 47% reduction in the incidence of threatening retinopathy.[36] Recently, a 23-year follow-up of the latter study showed that early lifestyle intervention was associated with a decrease in the cumulative incidence of cardiovascular and all-cause mortality.[37] Current ADA recommendations for the management of (pre)diabetes reflect these observations and risk indicators for (pre)diabetes screening are needed and proposed.[8] Notably, among subjects with severe periodontitis, we found that more than 18% of the subjects, who were unaware of the presence of diabetes, had HbA1c values exceeding the 6.5% (48 mmol/mol) threshold. This proportion is almost two times greater than those observed for patients with mild/moderate periodontitis (9.9%) and for subjects without periodontitis (8.5%). This confirms the assumption that severe periodontitis could be an early sign of undiagnosed diabetes. In this respect, the presence of severe periodontitis might be indicative of metabolic dysregulation and by the identification of diabetes, treatment of this disease can be initiated, which is also relevant for the successful treatment of periodontitis. We expect that a good collaboration between dentists and diabetologists will lead to the best treatment results.

One recent study used a point-of-care (POC) HbA1c assessment by means of a finger-stick blood sample but employed a benchtop analyzer.[38] Although this test obtains rapid results, the accuracy compared with values obtained by the standard assessment of HbA1c is questionable.[39] In contrast, our finger-stick and Whatman paper collection method and the standard immunoturbidimetric assessment of HbA1c on an Abbott ci8200 clinical chemistry analyzer[26] showed a very high correlation with the venipuncture collection method and subsequent HbA1c measurement (r=0.99). Despite a less accurate HbA1c determination, the results of the recent study[38] corroborate our findings that a substantial number of patients with suspected new diabetes in the periodontitis group can be found. A higher frequency of patients with suspected new diabetes in the periodontitis group in our study can be explained by the higher accuracy of our method for HbA1c determination and a clear case definition for subjects without or with mild/moderate or severe periodontitis. Notably, subjects with severe periodontitis showed a high frequency of suspected new diabetes cases, and the applied ADA case definition may therefore be very useful in general practice. In our study, compared with the recent publication,[38] the control and periodontitis groups were comparable regarding age and ethnic origin; these factors have been considered important for diabetes screening.[8]

The prevalence of suspected diabetes in the control group (10.1%) in this study, as measured by HbA1c, is high compared with the overall estimated prevalence in the Netherlands (5.45%).[28] An obvious explanation could be that our study population, derived from a dental school, is not representative of the Dutch population. Another reason might be that the national prevalence is actually an underestimation; since diabetes is often asymptomatic in its early stages, it may remain undiagnosed for many years.[40] In addition, it is possible that the current use of HbA1c levels results in a higher prevalence compared with the prevalence based on the traditional parameter plasma glucose levels, such as fasting plasma glucose levels and/or the oral glucose tolerance test. The recently adopted diagnosis of diabetes by HbA1c has been proposed by the ADA,[8] and the advantages and disadvantages for HbA1c as a diagnostic marker have been extensively discussed in the literature.[30 41–45] However, most of the studies show that even the use of HbA1c levels may result in an underestimation of diabetes prevalence. Nevertheless, a higher cut-off of HbA1c of ≥7.0% (≥53 mmol/mol, instead of ≥6.5% (≥48 mmol/mol)) has been proposed to exclude a possible false-positive diagnosis.[29 30] When applying this threshold, the prevalence of subjects with HbA1c levels of ≥7.0% (≥53 mmol/mol) in the control group was 3.7%, and this can be considered to be in agreement with the overall estimated prevalence of diabetes in the Netherlands. Nevertheless, applying the threshold ≥7% (≥53 mmol/mol), the prevalence of subjects with diabetes was clearly higher in those with mild/moderate periodontitis (7.1%) and with severe periodontitis (12.8%). Interestingly, the results show that half of the subjects classified as having diabetes, using a threshold of ≥6.5% (≥48 mmol/mol), do have HbA1c levels in the range of 6.5–7% (48–53 mmol/mol), confirming that periodontitis is a useful risk indicator for the screening of early diabetes. The early diagnosis and intervention of (pre)diabetes prevent the common microvascular and macrovascular complications[6] and are cost-effective.[7] In addition, it can be suggested that the early diagnosis and treatment of (pre)diabetes may also benefit the treatment of periodontitis.

A dental office that treats patients with severe periodontitis is a suitable location for screening for (pre) diabetes; a considerable number of suspected new diabetes cases were identified and indicated that periodontitis is an early sign of diabetes mellitus.

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