Periodontal findings in individuals with newly identified pre-diabetes or diabetes mellitus


Abstract

Aim: To assess the periodontal status and number of missing teeth in patients with newly identified pre-diabetes or diabetes mellitus.

Methods: A total of 1097 subjects with previously undiagnosed diabetes were available for study, and were categorized into normoglycaemic, potentially pre-diabetes or potentially diabetes groups based on a point-of-care (POC) HbA1c test.

Results: In fully adjusted models, significant differences were observed between all groups for the per cent of teeth with at least one site with a probing depth of ≥5 mm. For bleeding on probing, there were significant differences between diabetes and pre-diabetes (p = 0.001), and between diabetes and normoglycaemic groups (p = 0.002). For missing teeth, there were significant differences between the pre-diabetes and normoglycaemic groups (p = 0.034), and the diabetes and normoglycaemic groups (p = 0.004).

Conclusions: Individuals with previously unidentified pre-diabetes demonstrate a level of periodontal destruction between that observed for normoglycaemic individuals and persons with diabetes. These data emphasize the association of oral findings to dysglycaemia, and suggest that periodontal disease and tooth loss can be early complications of diabetes mellitus.

Conflict of interest and source of funding

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observation that severe periodontitis adversely affects metabolic control in patients with diabetes. A number of meta-analyses have demonstrated that periodontal therapy can improve metabolic control as assessed by a reduction in glycosylated haemoglobin (HbA1c) of approximately 0.4% (Simpson et al. 2010, Teeuw et al. 2010, Engebretson & Kocher 2013), although this conclusion was not supported by a recent multicentre randomized clinical trial (Engebretson et al. 2013). Nevertheless, the importance of the periodontal disease—diabetes mellitus association is further emphasized by the observation that periodontal disease has been identified as a risk factor for death from renal or cardiac causes in patients with type 2 diabetes (Saremi et al. 2005), development of macroalbuminuria and end-stage renal disease in these patients (Shults et al. 2007), as well as the development of incident diabetes (Demmer et al. 2008).

In two earlier reports, the results of a clinical study were presented that sought to identify patients with previously unidentified dysglycaemia (diabetes mellitus or pre-diabetes) in adults seeking dental services (Lalla et al. 2011, 2013). All participants received a full-mouth periodontal examination, as well as a point-of-care (POC) assessment of HbA1c. Therefore, this study provides the opportunity to examine the relationship of newly identified and untreated dysglycaemia to periodontal status. Here, we report on the relationship of clinical periodontal parameters to glycaemic status in the 1097 patients who participated in the study.

Materials and Methods

The clinical protocol has previously been described in detail (Lalla et al. 2011, 2013). Approval was obtained from the Columbia University Institutional Review Board, conforming to guidelines established by STROBE. Written consent was obtained from all study participants. Entry criteria included never having been told to have diabetes or pre-diabetes, ≥40 years old if white, non-Hispanic and ≥30 years old if non-white or Hispanic. In addition, participants were included if they reported at least one of four risk factors for diabetes: had a first-degree relative with diabetes, had been told they had hypertension, hypercholesterolaemia or that they were overweight or obese.

Participants who met the entry criteria and agreed to participate in the study then received a periodontal examination, including recording of missing teeth, and probing depth measurement and assessment of bleeding following probing at six sites per tooth, excluding third molars. The clinical data were collected by one examiner (SB) prior to POC testing for HbA1c, and blood collection for laboratory fasting plasma glucose (FPG) or HbA1c. Specifically, a fingerstick blood sample was collected from all participants for chairside assessment of per cent HbA1c using the DCA 2000 Plus (Bayer Healthcare, Tarrytown, NY, USA). The study had two cohorts who were assessed identically except for the final laboratory test to define glycaemic status. The first 506 participants returned for collection of a fasting venous blood sample to assess the FPG concentration. The second group of 591 subjects had a venous blood sample drawn on the same day to determine the laboratory per cent HbA1c. In the previous reports (Lalla et al. 2011, 2013), participants were categorized by the FPG or laboratory HbA1c based on criteria of the American Diabetes Association (American Diabetes Association 2014). Here, glycaemic status was defined using the POC HbA1c data since all participants in both groups were evaluated using this test.

Statistical analysis

Continuous variables were compared using ANOVA F test and categorical variables were compared using chi-squared test. Per cent of sites with bleeding on probing was analysed using a linear regression model; per cent of teeth with pocket depth of 5 mm or greater was analysed using a Beta regression model with logit link; number of missing teeth was analysed using a zero-inflated Poisson model. All three models used glycaemic status (normoglycaemia, pre-diabetes, diabetes) as the main predictor, controlling for age, sex, ethnicity, smoking, overweight/obesity, and elevated cholesterol. For per cent of teeth with a pocket depth of 5 mm or greater, the analysis was also controlled for the number of teeth present. The analysis was conducted using SAS version 9.2 and plots were generated in R version 3.0.1. p-values <0.05 were considered statistically significant.

Results

Correlation of POC HbA1c with Laboratory Measures of HbA1c and FPG

The first cohort of 506 participants was tested for glycaemic status by FPG and POC HbA1c. The Pearson correlation between the two tests was 0.80 and was statistically significant (p < 0.001; Fig. 1a). The second cohort of 591 subjects was tested with a laboratory HbA1c (high-performance liquid chromatography) and the POC HbA1c test. For these subjects, the Pearson’s correlation between these two measures of HbA1c was 0.93 (p < 0.001; Fig. 1b).

Subject characteristics

In Table 1, study participants are presented in three groups based on the POC HbA1c result at the dental examination visit. Fifty-five per cent were in the normoglycaemic range, 37.3% were in the pre-diabetes range, and 7.7% in the diabetes range. In this unadjusted analysis, there were differences between groups in terms of age (participants with dysglycaemia were older), and race (the per cent of participants who were in the diabetes category was greater for African-Americans than for whites or Asians).

The number of missing teeth increased with increasing dysglycaemia. Individuals classified in the diabetes group had more missing teeth than those with pre-diabetes, and those with pre-diabetes had more missing teeth than individuals classified as normoglycaemic. The per cent of sites with bleeding on probing was greatest for subjects in the diabetes category. The per cent of teeth with at least one site with a probing depth of 5 mm or more was greatest for patients with diabetes, followed by pre-diabetes and then
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Three groups as mean HbA1c: <5.7%; potential pre-diabetes: 5.7-6.4%; potential diabetes: ≥6.5%. Data are shown as mean ± SD or n (%). Overall p-values are from ANOVA test or χ² test, comparing all three groups.

<table>
<thead>
<tr>
<th>Subject characteristic</th>
<th>Normal POC HbA1c (%)</th>
<th>Potential Pre-diabetes (%)</th>
<th>Potential diabetes (%)</th>
<th>Overall p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>603 (55.0)</td>
<td>409 (37.3)</td>
<td>85 (7.7)</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>50.8 ± 12.0</td>
<td>55.7 ± 11.4*</td>
<td>59.1 ± 12.5*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Gender, female</td>
<td>374 (62.0)</td>
<td>279 (68.2)*</td>
<td>54 (63.5)</td>
<td>0.13</td>
</tr>
<tr>
<td>Ethnicity, Hispanic</td>
<td>395 (65.5)</td>
<td>283 (69.2)</td>
<td>59 (69.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>112 (18.6)</td>
<td>42 (10.3)</td>
<td>4 (4.7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African American</td>
<td>91 (15.1)</td>
<td>78 (19.1)</td>
<td>21 (24.7)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>6 (1.0)</td>
<td>7 (1.7)</td>
<td>2 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Other§</td>
<td>394 (65.3)</td>
<td>282 (69.0)</td>
<td>58 (68.2)</td>
<td></td>
</tr>
<tr>
<td>Number of missing teeth¶</td>
<td>5.8 ± 6.2</td>
<td>7.4 ± 6.7*</td>
<td>9.3 ± 7.1*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Per cent of sites with bleeding on probing§</td>
<td>50.6 ± 22.6</td>
<td>49.6 ± 22.7</td>
<td>58.3 ± 23.6*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Per cent of teeth with at least one pocket with probing depth ≥5 mm</td>
<td>21.6 ± 26.1</td>
<td>25.4 ± 26.7*</td>
<td>35.9 ± 28.0*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Self-reported family history of diabetes</td>
<td>337 (55.9)</td>
<td>224 (54.8)</td>
<td>52 (61.2)</td>
<td>0.56</td>
</tr>
<tr>
<td>Self-reported hypertension</td>
<td>168 (27.9)</td>
<td>176 (43.0)*</td>
<td>42 (49.4)*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Self-reported high cholesterol</td>
<td>201 (33.3)</td>
<td>180 (44.0)*</td>
<td>37 (43.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Self-reported overweight/obesity</td>
<td>442 (73.3)</td>
<td>335 (81.9)*</td>
<td>76 (89.4)*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>361 (60.4)</td>
<td>262 (64.5)</td>
<td>51 (60.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Current smoker</td>
<td>97 (16.2)</td>
<td>52 (12.8)</td>
<td>15 (17.7)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>140 (23.4)</td>
<td>92 (22.7)</td>
<td>19 (22.4)</td>
<td></td>
</tr>
</tbody>
</table>

§Statistically significantly different compared to normal HbA1c.
¶statistically significantly different compared to pre-diabetes.
*The vast majority of Hispanic subjects refused to self-identify with any of the racial groups, choosing the option “other” or “unknown”.
¶Out of 28 teeth.
*Fully edentulous subjects excluded.

Table 1. Subject characteristics by POC HbA1c test outcome (N = 1097). Normal POC HbA1c: <5.7%; potential pre-diabetes: 5.7-6.4%; potential diabetes: ≥6.5%. Data are shown as mean ± SD or n (%). Overall p-values are from ANOVA test or χ² test, comparing all three groups.

Statistically significantly different compared to normal HbA1c.
†Statistically significantly different compared to pre-diabetes.

The vast majority of Hispanic subjects refused to self-identify with any of the racial groups, choosing the option “other” or “unknown”.

†Out of 28 teeth.

Fully edentulous subjects excluded.

the normoglycaemic group. For other health variables, differences were seen between groups for self-reported hypertension, elevated cholesterol, obesity/overweight, but not self-reported family history of diabetes or history of smoking. Lastly, no differences were observed when analyzed by sex.

When the per cent of teeth with at least one deep pocket (≥5 mm) was further examined by the number of the teeth present, an interesting trend was observed (Fig. 2). When most teeth (20-28) were present, there was a clear positive association of the per cent of teeth with deep pockets, and increasing dysglycaemia. This trend was less pronounced for the individuals with a compromised dentition (10-19 teeth). For individuals with only one to nine teeth present, the per cent of teeth with deep pockets was comparable for the pre-diabetes and diabetes groups, which were greater than that for individuals in the normoglycaemic group.

Using regression analysis (Table 2), in fully adjusted models, significant differences were seen between all groups for the per cent of teeth with probing depths of 5 mm and greater. Significant differences were also observed for bleeding on probing between pre-diabetes and diabetes (p = 0.001) and diabetes and health (p = 0.002). For missing teeth, there were significant differences between the pre-diabetes and normoglycaemic groups (p = 0.034), and the diabetes and normoglycaemic groups (p = 0.004).

Discussion

This study is unique in reporting periodontal findings from individuals with newly identified dysglycaemia (both pre-diabetes and diabetes), which have not been modified by medical treatment. The results are consistent with the well-described relationship between established diabetes mellitus and severity of periodontal disease. In an unadjusted analysis, as compared to normoglycaemic adults, individuals in the pre-diabetes range demonstrated significantly increased periodontal disease as assessed by the per cent of teeth with at least one pocket ≥5 mm, and the number of missing teeth. Differences between diabetes and pre-diabetes and diabetes and health were observed for the per cent of teeth with at least one site with a probing depth greater than 5 mm and the number of missing teeth. In the fully adjusted
models, for the three clinical variables, the differences among the three groups were most pronounced for the percentage of teeth with a probing depth of 5 mm and greater.

Pre-diabetes is present when the serum glucose concentration or HbA1c is elevated, but not to the level that defines diabetes mellitus. It can be defined by impaired fasting glucose, impaired glucose tolerance and glycosylated haemoglobin. Pre-diabetes is generally considered to be a reversible metabolic condition (Garnett et al. 2010). Evidence suggests, however, that clinical complications occur when this condition is present, including reduced lung function (Li et al. 2013), neuropathy (Divisova et al. 2012, Bongaerts et al. 2013) and retinopathy (Al Shafaee et al. 2011). Nephropathy is considered an early complication of diabetes, and evidence suggests that pre-diabetes is associated with early nephropathy. A community-based study of the prevalence of chronic kidney disease and pre-diabetes (defined by FPG) indicated that insulin resistance and pre-diabetes were risk factors for chronic kidney disease (Gu et al. 2013). Furthermore, individuals with pre-diabetes have been shown to be at increased risk of microalbuminuria (Bahar et al. 2013).

There is some previous evidence of an association between periodontal disease and pre-diabetes. Pre-diabetes as defined by impaired glucose tolerance was associated with a higher mean pocket depth (Saito et al. 2004, 2005) and greater alveolar bone loss in men (Saito et al. 2006). Of note, the increase in mean probing depth observed in women with pre-diabetes was related to measures of obesity, including body mass index, per cent body fat, and the waist-to-hip ratio (Saito et al. 2005). A study of bleeding following probing in individuals who had not received a diagnosis of diabetes revealed that patients above the median bleeding percentage demonstrated an increased likelihood of impaired fasting glucose (odds ratio = 5.5, 95% CI 1.2–25.3) or impaired glucose tolerance (odds ratio 3.6, 95% CI 1.0–13.2; Andriankaja & Joshipura 2014). In another study, periodontal parameters were assessed in three groups of individuals: (i) pre-diabetes (defined by FPG or HbA1c), (ii) previously identified pre-diabetes which was controlled with dietary modification and (iii) normal controls. The individuals with existing pre-diabetes demonstrated more severe periodontal disease (probing depth, attachment loss, bleeding on probing, and radiographically determined alveolar bone loss) than either the formerly pre-diabetic patients or healthy controls. Furthermore, self-reported measures of oral diseases (including bleeding, pain upon chewing, dry mouth, and oral burning) were also more common in the pre-diabetic versus the former pre-diabetic patients or healthy controls (Javed et al. 2014). Furthermore, self-reported measures of oral diseases (including bleeding, pain upon chewing, dry mouth, and oral burning) were also more common in the pre-diabetic versus the former pre-diabetic patients or healthy controls. These findings suggest that objective and subjective signs and symptoms of periodontal disease and other oral disorders were worse in patients with pre-diabetes versus healthy individuals, but those oral/
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Periodontal changes can be reversed with improved glycaemic control.

The data reported here extend those findings by noting that in fully adjusted models, the per cent of sites with bleeding on probing, the per cent of teeth with deep pockets and the number of missing teeth were all significantly increased with newly identified dysglycaemia. Furthermore, in an adjusted regression model, categorizing patients using POC HbA1c to define their metabolic status (healthy, pre-diabetes or diabetes), the per cent of sites demonstrating bleeding on probing was greatest for individuals in the diabetes group versus both the pre-diabetes and healthy groups. Significant differences were noted in the per cent of sites with deep pockets between health and pre-diabetes, pre-diabetes and diabetes and health and diabetes. For missing teeth, there was a difference between health and diabetes, and health and pre-diabetes, but not pre-diabetes and diabetes. While diabetes is associated with increased prevalence of periodontal disease (Lalla & Papapanou 2011, Taylor et al. 2013) and increased tooth loss (Patel et al. 2013) the data presented here indicate that pre-diabetes is also associated with significant changes in periodontal pathology.

The relationship of periodontal disease to dysglycaemia was also examined in relationship to the number of remaining teeth in the mouth. A positive association of the per cent of teeth with deep pockets to increasing dysglycaemia was seen for all three categories (≥20 teeth, 10–19 teeth, ≤9 teeth), indicating that when dysglycaemia is present, all teeth in the mouth are at risk for increased periodontal disease, not just those that are recognized to be at greatest risk for periodontal disease (i.e. molars).

The finding that the severity of periodontal disease in patients with pre-diabetes is between that of individuals who are normoglycaemic and those who would be classified as having diabetes mellitus suggests that the pathologic processes that account for periodontal pathology and other aspects of diabetes-associated morbidity are dependent on a common risk factor, likely hyperglycaemia-induced inflammation. One important mechanism is the binding of advanced glycation end products to their receptors, with an increased inflammatory response (Lalla et al. 1998, 2000). Increased levels of inflammatory markers have been reported in both gingival fluid (Duarte et al. 2014) and saliva (Yoon et al. 2012) from patients with type 2 diabetes mellitus.

In a study of periodontal findings in children and adolescents with diabetes mellitus, clinical attachment loss and bleeding following probing were significantly greater in diabetes patients versus age-matched non-diabetic controls (Lalla et al. 2007). Furthermore, the patients with diabetes did not demonstrate microvascular complications as assessed by fundus photography and serum markers of kidney function (unpublished data). Those findings suggested that periodontal disease may be an early indicator of complications associated with dysglycaemia. This study extends and supports that conclusion by identifying increased periodontal disease and tooth loss in individuals with newly identified pre-diabetes or diabetes, previously unaware of their status.

The concentration of HbA1c in serum has been shown to identify the risk for the microvascular complications (retinopathy and neuropathy; Fullerton et al. 2014). In this report, we classified individuals as normoglycaemic, pre-diabetes or diabetes based on the POC HbA1c findings. While the concentration of HbA1c in blood is now one of the criteria for diagnosis of diabetes mellitus (American Diabetes Association 2014), laboratory analysis (high-performance liquid chromatography) is required, and must be repeated for a diagnosis. Nevertheless, the reported results suggest that a POC HbA1c test is a potentially valuable adjunct to comprehensive dental care that can help identify patients at risk for diabetes, and explain early signs of periodontal disease and premature tooth loss.

A strength of this study is the inclusion of patients who were not previously identified as having diabetes mellitus or pre-diabetes, and were not treated medically for hyperglycaemia, and as new patients to the clinic who were seeking dental care, they had not recently received dental/periodontal treatment. This reduces the potentially important influence of medical and dental treatment on the observed hyperglycaemia–periodontal disease relationship.

Shortcomings of this study include the cross-sectional design. Cause and effect cannot be determined. In addition, participants in this study were residents of northern Manhattan, and more than two-thirds were Hispanic, so these findings are specific to our population, and must be confirmed in other racial and ethnic groups.

In conclusion, the present findings indicate that individuals with newly identified pre-diabetes or diabetes are at increased risk of periodontal disease and tooth loss. The association of increased oral disease with pre-diabetes again supports the concept that periodontal/oral pathology are early clinical manifestations of dysglycaemia, and therefore oral health care providers can play an important role in early identification of patients at risk for, or with, diabetes mellitus. Oral health care providers need to be prepared to discuss both pre-diabetes and diabetes with patients, including lifestyle changes to modify risk, and when appropriate refer them for care to a medical provider. This interdisciplinary approach to health care will have a beneficial impact on both the general health and oral health of affected individuals.

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Clinical Relevance

**Scientific rationale for the study:** Diabetes mellitus is a recognized risk factor for periodontal disease and tooth loss. This study sought to determine if individuals with pre-diabetes also demonstrate evidence of periodontal destruction and increased tooth loss.

**Principal findings:** In a population of 1097 individuals seeking dental services, 55% would be classified as normoglycaemic, 37.3% as potentially pre-diabetic and 7.7% as potentially diabetic. Prevalence of periodontal disease and tooth loss were greatest for individuals with diabetes, followed by those with prediabetes and then the normoglycaemic individuals.

**Practical Implications:** Pre-diabetes is a risk factor for diabetes, and is considered metabolically reversible. However, these data indicate that increased prevalence of periodontal disease and tooth loss occurs in individuals with pre-diabetes. Considering the prevalence of pre-diabetes and diabetes, patients with evidence of periodontal disease should be assessed for dysglycemia.

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