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Association of hyperglycemia with periodontal status: results of the Northern Finland Birth Cohort 1966 study

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Abstract

Aim: To investigate the association of hyperglycemia and changes in glycemic control with periodontal status in non-diabetic individuals.

Materials and methods: A sub-population ($n = 647$) of the Northern Finland Birth Cohort 1966 (University of Oulu 1966) was studied. We categorized long-term glucose balance based on fasting plasma glucose (FPG) at ages 31 and 46: FPG < 5.0 mmol/l (strict normoglycemia), FPG 5.0–5.59 mmol/l (slightly elevated FPG) and FPG 5.6–6.9 mmol/l (prediabetes). Probing pocket depth (PPD) and alveolar bone level (BL) data were collected at age 46. Relative risks (RR, 95% CI) were estimated using Poisson regression models.

Results: Periodontal status was poorer in individuals whose glucose balance worsened from age 31 to 46 years than in those with a stable glucose balance. In the case of strict normoglycemia at

age 31 and slightly elevated FPG or prediabetes at age 46, the RRs for PPD ≥ 4 mm were 1.8 (95% CI 1.4–2.2) and 2.8 (95% CI 2.0–3.8) and for BL ≥ 5 mm 1.1 (95% CI 0.8–1.4) and 1.8 (95% CI 1.2–2.8), respectively.

Conclusion: The results of this population based cohort study suggest that impairment in glucose control in non-diabetic individuals is associated with periodontal pocketing and alveolar bone loss.

Clinical Relevance:

Scientific rationale for the study: A number of cross-sectional studies show that prediabetes is associated with periodontitis but information based on longitudinal studies is scarce. Moreover, the effects of early hyperglycemia under the threshold for prediabetes on the periodontium are largely unknown.

Principal findings: This study provided evidence that prediabetes and even slightly elevated fasting plasma glucose levels may be associated with ≥ 4 mm probing pocket depths.

Practical implications: Future studies using more accurate monitoring of dysglycemia are needed to confirm the association of early hyperglycemia with periodontal status.

Introduction

Prediabetes denotes the precursor stage of diabetes mellitus characterized by fasting plasma glucose levels which are elevated but below the threshold for the diagnosis of diabetes. Prediabetes has been defined using several measures, including impaired fasting glucose, impaired glucose tolerance and elevated glycated hemoglobin (American Diabetes Association 2017). The prevalence of prediabetes is dependent on which diagnostic test is used, and population characteristics such as age and gender distribution, and ethnic composition. Prediabetes is common; based on the definition by American Diabetes Association (ADA) (Yip et al. 2017), it has been reported to affect 48.1% of the Asian population and 58.9% of European Caucasian adults.

From the point of view of public health, it is important to keep in mind that up to 70% of individuals with prediabetes have been estimated to develop diabetes (Nathan et al. 2007). The clinical complications of diabetes mellitus include micro- and macrovascular complications such as cardiovascular disease, retinopathy, neuropathy and nephropathy. The underlying mechanisms in the pathogenesis of these complications are that subjects with hyperglycemia have multiple biological abnormalities, such as an imbalance of cytokines and adipokines, oxidative stress and accumulation of advanced glycation end products (AGEs) and their receptor RAGE in tissues (King 2008; Giacco and Brownlee 2010). Subjects with hyperglycemia also have impaired tissue repair and poor wound healing (Baltzis et al. 2014). Many of the above biological effects of hyperglycemia are also observable in periodontal tissues (Polak and Shapira 2018) and, in fact, periodontitis has been declared the 'sixth complication' of diabetes mellitus (Løe 1993).

In view of the overall high prevalence of both prediabetes and periodontal infection, it is important to study whether the risk for periodontal tissue destruction is increased in non-diabetic individuals with elevated fasting plasma glucose. Most of the earlier studies are cross-sectional, and report positive associations between prediabetes and periodontitis (Hong et al. 2016; Pérez et al. 2017; Lamster et al. 2014). To our knowledge, only two longitudinal studies exist in this area; one of them reported an increased incidence of periodontal infection in prediabetic individuals (Chiu et al. 2015) and the other one in individuals with insulin resistance/disturbed beta cell function

(Timonen et al. 2013). The strength of these longitudinal studies is that they took into account the temporal sequence between the periodontal and the dysglycemic conditions. In this study, we hypothesized that fasting plasma glucose level is associated with periodontal status in non-diabetic individuals. Subsequently, we investigated whether the changes in fasting plasma glucose level between ages 31 and 46 were associated with the number of sites with ≥ 4 mm probing pocket depth and ≥ 5 mm alveolar bone level at age 46.

Materials and methods

The Northern Finland Birth Cohort 1966 (NFBC1966) is a cohort study that examined the health and well-being of individuals born in 1966 in the two northernmost provinces in Finland (Oulu and Lapland). In the 2012–2013 data collection, when the subjects were 46-year-olds, an oral health examination was conducted for the first time on 1,964 participants living in the city of Oulu or within a 100 km radius of Oulu. Prior to that, general health data were gathered 15 years earlier when the cohort was 31 years old. In this study, we used the periodontal data from the examination at age 46 and the fasting plasma glucose (FPG) data from the examinations at ages 31 and 46. Subjects with manifest diabetes mellitus (DM 1 and 2), rheumatic and inflammatory intestinal and lung diseases were excluded; these diagnoses were obtained from the registries of the Finnish Institute for Health and Welfare (THL). In addition, individuals with DM 2 screened in the oral glucose tolerance test of the age 46 follow-up study were excluded. Data on smoking history were collected using a questionnaire and only never-smokers were included in the current analyses ($n = 647$). The study was approved by the Ethical Committee of the Hospital District of Northern Ostrobothnia.

Periodontal examination

Periodontal data, including dental plaque, probing pocket depth (PPD) and bleeding on probing (BOP) from all teeth excluding third molars and residual roots were collected by seven calibrated dentists using a mouth mirror and a ball-pointed periodontal probe with 2 mm graduations (LM 8-520B, Lääkintämuovi, Finland). Before conducting of the study the examiners underwent training on periodontal examination in volunteer subjects under the supervision of an experienced periodontist (TT). The training included a calibration of probing pressure of 25 g using a letter scale. The examiners also practiced the application of periodontal measurement criteria in a group

of 12 individuals. Immediate feedback was given to the questions raised by the examiners in these exercises and also to the questions/inquiries that were entered in writing in the shared research diary during the field work. Replicate periodontal measurements in the cohort subjects were used to calculate the agreement percentages and the inter-examiner and intra-examiner Cohen's kappa values (95% CI) in 108 and 129 individuals, respectively. The examiner with the most clinical experience served as the 'gold standard' examiner.

The absence/presence of plaque was examined from buccal surfaces of the teeth (single score per tooth) and categorized as follows: 1 = no plaque, 2 = visible plaque or plaque, as measured by touching the tooth surface lightly with the periodontal probe (Table 3a).

Probing pocket depths (PPD) were measured at four sites per tooth (mesiobuccal, midbuccal, distobuccal, midoral). Probing force (25 g) was calibrated using a letter scale before examining each participant. The inter- and intra-examiner agreements for PPD measurements were 70% and 81% and the Cohen's kappa values were 0.39 (95% CI 0.34–0.43) and 0.61 (95% CI 0.58–0.64), respectively.

Bleeding on periodontal probing (BOP) at the four sites was registered (Table 3a).

Radiographic examination

Alveolar bone level (BL) on approximal sites of all teeth was measured using panoramic radiographs by a dental hygienist. Panoramic radiographs were available of 568 never-smoking subjects. The mean number ($\pm$ SD) of measurable sites per individual was 33.0 ($\pm$ 9.1). The distance from the cemento-enamel junction (CEJ) to the point where the periodontal ligament space still remained at its normal width was measured in millimeters. Any sites where the CEJ or the alveolar crest could not be identified were excluded. Reproducibility was assessed by replicate measurements using the radiographs of the cohort participants. The supervising periodontist (TT) served as the reference examiner. The inter- and intra-examiner agreements for BL measurements were 67% and 70% and the Cohen's kappa values were 0.54 (95% CI 0.50–0.57) and 0.59 (95% CI 0.54–0.63) respectively.

Fasting plasma glucose (FPG)

Determination of the glucose balance was based on the FPG levels in the subjects' venous blood samples. We used two parallel criteria to determine different FPG categories separately at ages 31 and 46. First we categorized the subjects into two groups based on the ADA criteria; those with normoglycemia (FPG < 5.6 mmol/l) and those with prediabetes (FPG 5.6–6.9 mmol/l) (American Diabetes Association 2017). Next the normoglycemic individuals were further categorized into two groups: individuals with FPG < 5.0 mmol/l vs. FPG 5.0–5.59 mmol/l. Subsequently, the following three categories existed: FPG < 5.0 mmol/l (strict normoglycemia), FPG 5.0–5.59 mmol/l (slightly elevated FPG) and FPG 5.6–6.9 mmol/l (prediabetes). The above FPG categorizations at ages 31 and 46 were then combined to determine the long-term glucose balance – either stable or worsened – and the following two-class or three-class categorizations were made for the statistical analyses (Table 4).

Stable glucose balance; an individual stayed in the same FPG category at ages 31 and 46

The two-class categorization (ADA):

- FPG < 5.6 mmol/l (normoglycemia), $n = 440$ (reference group),
- FPG 5.6–6.9 mmol/l (prediabetes), $n = 24$,

The three-class categorization:

- FPG < 5.0 mmol/l (strict normoglycemia), $n = 109$ (reference group),
- FPG 5.0–5.59 mmol/l (slightly elevated FPG), $n = 119$,
- FPG 5.6–6.9 mmol/l (prediabetes), $n = 24$.

Worsened glucose balance; a shift to poorer glucose balance from age 31 to 46 occurred:

The two-class categorization (ADA):

- FPG < 5.6 mmol/l at ages 31 and 46, $n = 440$ (reference group),
- FPG < 5.6 mmol/l (normoglycemia) at 31 years and FPG 5.6–6.9 mmol/l (prediabetes) at age 46, $n = 149$,

The three-class categorization:

- FPG < 5.0 mmol/l at ages 31 and 46, $n = 109$ (reference group),
- FPG < 5.0 mmol/l (strict normoglycemia) at age 31 and FPG 5.0–5.59 mmol/l (slightly elevated FPG) at age 46, $n = 179$,

- FPG < 5.0 mmol/l (strict normoglycemia) at age 31 and FPG 5.6–6.9 mmol/l (prediabetes) at age 46, $n = 56$.

Lipid profile

Total cholesterol, triglycerides and high-density lipoprotein (HDL) were measured at age 46 from the subjects' venous blood samples and used in the analyses as continuous variables (mmol/l) (Tables 1–3).

Other variables

The data on socio-demographics and health behavior were based on a questionnaire at age 46. Education was categorized into three categories: basic (vocational school or lower), intermediate (graduated from a vocational college or university of applied sciences), and higher (graduated from a university) following the international standard classification of education (ISCED 1997). The frequency of physical exercise was categorized into four categories: 2–3 times a month or less frequently, once a week, 2–3 times a week, and daily or 4–6 times a week (Tammelin et al. 2003). The questions of oral health habits, toothbrushing frequency and time since the most recent dental visit, were based on the guidelines of the World Health Organization (2013). In this study, toothbrushing variable was categorized into four categories: twice a day or more often, once a day, and less frequently, and the most recent dental visit into four categories: less than 12 months ago, 1 year but less than 2 years ago, and 2 years or more ago. Alcohol consumption was used both as a continuous (g/day) and as a categorized variable: abstainers (0 g/day) and tertiles of alcohol users (< 3.0 g/day, 3.0–11.1 g/day, and > 11.1 g/day). Body mass index (BMI, kg/m²) was categorized into three categories: < 24.9, 25.0–29.9 and ≥ 30.0 (World Health Organization 2000).

Statistical analyses

In the analyses, the numbers of sites with PPD ≥ 4 mm and BL ≥ 5 mm were used as outcome variables (count variables). Relative risks (RR) and 95% confidence intervals (95% CI) were estimated using Poisson regression models (Table 4). The categories of individuals with FPG < 5.6 mmol/l (the two-class categorization) and < 5.0 mmol/l (the three-class categorization) at ages 31 and 46 were used as the reference category. Gender, BMI, education and plaque – all associated with both the outcome and the explanatory variable (FPG) (Tables 1, 2 and 3a) – were used as covariates; plaque as a continuous and the others as categorized variables. The number of

tooth sites was used as an offset variable. The analyses were carried out among the total population and among highly-educated individuals (graduated from a university or a university of applied sciences). The statistical analyses were done using the IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA).

Results

The basic characteristics of the study population are presented in Tables 1–3. As to the long-term glucose balance, the basic characteristics are presented in relation to the three-class categorization (Table 3a).

There were no essential differences in the mean number of teeth between the glucose balance categories (Table 3a). Of the 252 individuals who remained in the same glucose balance category at ages 31 and 46 109 individuals (43%) had FPG < 5.0 mmol/l, 119 (47%) had slightly elevated FPG (5.0–5.59 mmol/l) and 24 (10%) had prediabetes (FPG 5.6–6.9 mmol/l). Out of the 344 individuals whose FPG was < 5.0 mmol/l at age 31, 179 (52%) had slightly elevated FPG (5.0–5.59 mmol/l) and 56 (16%) developed prediabetes by the age of 46.

Overall, after adjusting for gender, BMI, education and plaque, and using the two-class (ADA) categorization of glucose balance, only weak if any associations were found between a stable long-term glucose balance and periodontal status (Table 4).

When the stable glucose balance was based on the three-class categorization, slightly elevated FPG (5.0–5.59 mmol/l) at ages 31 and 46 was associated with the number of sites with PPD $\geq$ 4 mm (RR 1.7, 95% CI 1.3–2.2). The corresponding figure for individuals belonging to the highly educated group was RR 3.3 (95% CI 2.4–4.5).

Those individuals whose FPG worsened from < 5.6 mmol/l at age 31 to 5.6–6.9 at age 46, i.e. those who developed prediabetes according to the two-class ADA categorization, were likely to have more sites with BL $\geq$ 5 mm (RR 1.3, 95% CI 1.0–1.6) when compared to those with FPG < 5.0 mmol/l at ages 31 and 46 (reference group) (Table 4). When using the three-class categorization, the RRs for PPD $\geq$ 4 mm were 1.8 (95% CI 1.4–2.2) and 2.8 (95% CI 2.0–3.8) in

individuals with a slightly elevated glucose level (FPG 5.0–5.59 mmol/l) and prediabetes (FPG 5.6–6.9 mmol/l), respectively, in the total population. The corresponding risk estimates (RRs) for $BL \geq 5$ mm were 1.1 (95% CI 0.8–1.4) and 1.8 (95% CI 1.2–2.8). In most cases the risk estimates (RRs) were lower among highly educated individuals when compared to the risk estimates among the total population.

In order to study the effect of other potential confounders such as HDL, triglycerides and alcohol consumption on the strength of the association, we made additional modelling. In these models, made among the total population we observed that the change in risk estimates was not more than 0.2 when the variables were added into the models one by one.

Discussion

In this study, an important finding was that individuals who developed prediabetes between the ages of 31 and 46 had an increased likelihood of periodontal pocketing and alveolar bone loss. A novel finding was that development of early hyperglycemia, in which the FPG levels were slightly elevated but still under the threshold for prediabetes, was associated with the number of sites with $PPD \geq 4$ mm. Our overall interpretation of these results is that the hyperglycemia-induced destructive changes in periodontal tissues may start already at FPG levels below the diagnostic threshold for diabetes mellitus and even at levels below the threshold for prediabetes.

The results are in line with an earlier longitudinal study, which was made in a 30–64-year-old never-smoking non-diabetic population with no ≥ 4 mm periodontal pockets at the baseline (Timonen et al. 2013). According to that study, impaired glucose metabolism, measured as insulin resistance and altered beta cell function, was associated with periodontal pocket formation during a 4-year period. Another, 5-year study by Chiu et al. (2015) in a 35–44-year-old population showed that individuals with prediabetes according to the ADA criteria (FPG 100–125 mg/dl corresponding to 5.6–6.9 mmol/l), but without previously diagnosed periodontal disease defined using the Community Periodontal Index (CPI) < 3 , had a 25% higher risk for developing deepened periodontal pockets (CPI ≥ 3) when compared to individuals with normoglycemia (FPG < 100 mg/dl corresponding to < 5.6 mmol/l). However, only weak if any associations between

prediabetes and periodontal status were found in the present study when the ADA criteria were used.

The hypothesis of the biologically plausible mechanisms between hyperglycemia and periodontal tissue destruction comes primarily from studies that investigate the link between diabetes mellitus and periodontitis. These studies reported hyperglycemia-associated microvascular changes, alterations in bone and connective tissue metabolism, and aberrant neutrophil functions as potential mechanisms (Mealey and Oates 2006), while the prevailing hypothesis emphasizes the role of a hyper-inflammatory state in the infected periodontal tissues in diabetes (Polak and Shapira 2018; Taylor et al. 2013). According to this hypothesis, the increased periodontal destruction during hyperglycemia can be explained by an exaggerated expression of a variety of pro-inflammatory mediators as a result of the accumulation of advanced glycosylation end products (AGEs) in periodontal tissues. In light of the present results, it appears that these effects on the periodontium could in some cases be observed already at FPG levels below the threshold for prediabetes.

Due to the complexity related to the shifts of individuals between various glucose balance categories over the course of time, we preferred two practical approaches – studying individuals with stable and worsened glucose balance (Table 4). Unlike the earlier longitudinal studies (Chiu et al. 2015; Timonen et al. 2013), in which the glucose balance was defined only at the baseline, the NFBC1966 study data made it possible for us to determine the long-term glucose balance based on FPG levels at two points of time, ages 31 and 46. Notwithstanding, the true exposure time by hyperglycemia could not be determined precisely, especially among those whose glucose balance worsened between the ages of 31 and 46.

In the case of a stable glucose balance, the risk for ≥ 4 mm probing pocket depths was increased in individuals who had slightly elevated glucose levels, whereas the risk was not increased in those who had prediabetes already at the age of 31 (Table 4). One explanation for the latter finding could be the improved health behaviors between ages 31 and 46 for individuals who were informed of their adverse findings within their bloodwork. Namely, individuals who had FPG > 5.6 mmol/l (prediabetes), high cholesterol, or low hemoglobin at age 31 were informed of these

findings and advised to contact their health care center or medical doctor for further clarifications on their health issues.

It is well known that the level of education is strongly related to lifestyle and health behavior (Clark & Royer 2013; Cutler & Lleras-Muney 2010). We also performed the analyses among individuals with a high level of education. The group of individuals with a low level of education was unfortunately too small for statistical analyses. In the case of a stable glucose balance, highly educated individuals whose FPG was slightly elevated had an exceptionally high risk for ≥ 4 mm probing pocket depths (RR 3.3). It is unclear whether the observed relative risk represents the true value related to elevated FPG in this limited sample or whether it is a random finding or a finding related to another, unexamined variable. It could be expected that restriction to the highly educated group would produce less biased risk estimates than those obtained in the total population because the study population is more homogenous.

Obesity has been associated with periodontitis in earlier studies (Chaffee & Weston 2010). Obesity also contributes to the development of hyperglycemia via insulin resistance and impaired pancreatic beta-cell function (Grundy 2016, Lauterbach & Wunderlich 2017). In order to control for the confounding effect of obesity we used BMI as a covariate in the regression models and carried out the analyses among non-obese individuals (BMI < 30) (data not shown). We also studied the confounding effect of HDL, triglycerides and alcohol consumption by adding them into the regression models. These complementary analyses showed that BMI, HDL, triglycerides and alcohol consumption had no essential effect on the results. In addition, it is worth noting that the number of teeth was quite high and similar between the various categories of glucose balance. To avoid biases due to smoking (Hujoel et al. 2002), all the analyses were conducted in a never-smoking population. We also took into account possible systemic inflammation by excluding individuals with systemic inflammatory diseases.

Since the oral examination was included in the NFBC study protocol for the first time when the cohort was 46 years old, the data did not permit us to determine the true incidence of pocket formation and alveolar bone loss. Another disadvantage was that instead of measuring six sites per tooth, *i.e.* three buccal and three palatal/lingual, as recommended by the current standards (Holftreter et al. 2017), only four sites were measured in this study. It is likely that by omitting

measurements on the approximal palatal/lingual sites we underestimated the extent and severity of periodontal infection (Susin et al. 2005). An obvious advantage in using continuous outcome variables in the regression analyses was that it reduced the effect of measurement error compared to a situation where the outcome is dichotomous. A shortcoming was that the overall reproducibility in the measurement of the outcome variables, numbers of sites with ≥ 4 mm probing pocket depth and ≥ 5 mm alveolar bone level, was on average only moderate.

Finally, in this study the associations of FPG with periodontal status were generally stronger in individuals whose FPG level worsened from age 31 to age 46 than in those who had elevated, although stable, FPG at both ages. It appeared that there were more obese individuals in the worsened than in the stable group (Table 3a) and the possible role of obesity in this context remains to be explored.

Within the limitations of this study we conclude that impairment in glucose control in non-diabetic individuals is potentially associated with periodontal pocketing and alveolar bone loss. Due to the uncertainty associated with the findings future studies are needed to verify the association of early hyperglycemia with periodontal status.

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Table 1. Basic characteristics of the study population; proportions/means and their standard deviations (SD) according to the number of probing pocket depths (PPD $\geq$ 4 mm)

	Number of sites with PPD $\geq$ 4 mm			
	0 <i>n</i> = 369	1–3 <i>n</i> = 184	4–7 <i>n</i> = 51	$\geq$ 8 <i>n</i> = 35
Gender, % (<i>n</i> = 639)				
Male	37.4	45.7	41.2	57.1
Female	62.6	54.3	58.8	42.9
Education, % (<i>n</i> = 623)				
Basic	24.9	32.4	28.0	54.3
Intermediate	51.7	47.7	54.0	37.1
Higher	23.5	19.9	18.0	8.6
Number of teeth, mean (SD) (<i>n</i> = 639)	27.0 (1.4)	27.0 (1.5)	27.0 (1.4)	26.9 (1.5)
Number of teeth with plaque, mean (SD) (<i>n</i> = 639)	4.9 (5.7)	5.5 (5.8)	7.8 (7.5)	10.7 (8.9)
Toothbrushing frequency, % (<i>n</i> = 638)				
Twice a day or more	75.8	72.8	72.5	45.7
Once a day	24.2	26.6	27.5	54.3
Less frequently	0.0	0.5	0.0	0.0
Most recent dental visit, % (<i>n</i> = 620)				
Less than 1 year ago	62.6	58.6	50.0	38.7
1–2 years ago	27.4	27.6	28.0	35.5
$\geq$ 3 years ago	10.1	13.8	22.0	25.8
Frequency of physical exercise, % (<i>n</i> = 632)				
2–3 times a month or less frequently	18.5	22.8	26.0	31.4
Once a week	20.2	20.0	24.0	14.3
2–3 times a week	43.3	41.7	38.0	34.3
Daily or 4–6 times a week	18.0	15.6	112.0	20.0
Alcohol consumption, % (<i>n</i> = 639)				
0 g / day	13.0	14.	11.8	11.4
0.001–3.0 g / day	39.8	34.8	31.4	40.0
> 3.0–11.1 g /day	28.2	31.5	29.4	25.7
> 11.1 g /day	19.0	19.6	27.5	22.9
BMI (kg/m²), % (<i>n</i> = 639)				
< 24.9	47.2	42.9	39.2	22.7

25–29.9	36.0	43.5	35.3	40.0
≥ 30	16.8	13.6	25.5	34.3
Total cholesterol (mmol/l), mean (SD) (<i>n</i> = 639)	5.3 (0.8)	5.2 (0.9)	5.3 (1.1)	5.5 (1.0)
HDL cholesterol (mmol/l), mean (SD) (<i>n</i> = 639)	1.6 (0.4)	1.6 (0.4)	1.7 (0.5)	1.5 (0.3)
Triglycerides (mmol/l), mean (SD) (<i>n</i> = 639)	1.1 (0.6)	1.1 (0.6)	1.1 (0.5)	1.6 (1.3)
Stable glucose balance, % (<i>n</i> = 249)				
FPG < 5.0 mmol/l at 31 and 46 years (ref.)	51.0	29.2	66.7	18.8
FPG 5.0–5.59 mmol/l at 31 and 46 years	40.9	58.3	33.3	68.8
FPG 5.6–6.9 (prediabetes) at 31 and 46 years	8.1	12.5	0.0	12.5
Worsened glucose balance, % (<i>n</i> = 340)				
FPG < 5.0 mmol/l at 31 and 46 years (ref.)	35.5	24.7	29.6	21.4
FPG < 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years	49.1	56.5	55.6	64.3
FPG < 5.0 mmol/l at 31 and 5.6–6.9 (prediabetes) at 46 years	15.4	18.8	14.8	14.3

BMI, body mass index; HDL, high density lipoprotein; FPG, fasting plasma glucose.

Table 2. Basic characteristics of the study population; proportions/means and their standard deviations (SD) according to the number of the sites with ≥ 5 mm alveolar bone level (BL)

	Number of sites with BL ≥ 5 mm		
	0 <i>n</i> = 307	1–3 <i>n</i> = 225	≥ 4 <i>n</i> = 36
Gender, % (<i>n</i> = 568)			
Male	39.1	44.4	47.2
Female	60.9	55.6	52.8
Education, % (<i>n</i> = 553)			
Basic	26.4	32.7	25.5
Intermediate	48.5	51.4	52.9
Higher	25.1	15.9	20.6
Number of teeth, mean (SD) (<i>n</i> = 566)	27.0 (1.4)	27.0 (1.5)	26.8 (1.7)
Number of teeth with plaque, mean (SD) (<i>n</i> = 564)	5.3 (6.1)	5.4 (5.9)	6.3 (6.4)
Toothbrushing frequency, % (<i>n</i> = 567)			
Twice a day or more	74.3	74.7	74.3
Once a day	25.4	25.3	25.7
Less frequently	0.3	0.0	0.0
Most recent dental visit, % (<i>n</i> = 549)			
Less than 1 year ago	62.4	52.1	60.0
1–2 years ago	24.4	33.8	28.6
≥ 3 years ago	13.2	14.2	11.4
Frequency of physical exercise, % (<i>n</i> = 561)			
2–3 times a month or less frequently	19.7	23.3	23.5
Once a week	20.1	22.4	11.8
2–3 times a week	44.1	38.1	47.1
Daily or 4–6 times a week	16.1	16.1	17.6
Alcohol consumption, % (<i>n</i> = 568)			
0 g / day	15.6	12.4	8.3
0.001–3.0 g / day	38.1	38.7	38.9
> 3.0–11.1 g /day	29.6	30.2	25.0
> 11.1 g /day	16.6	18.7	27.8
BMI (kg/m²), % (<i>n</i> = 568)			
< 24.9	44.3	43.1	50.0

25–29.9	36.8	40.9	27.8
≥ 30	18.9	16.0	22.2
Total cholesterol (mmol/l), mean (SD) (<i>n</i> = 568)	5.3 (0.9)	5.3 (0.8)	5.4 (1.1)
HDL cholesterol (mmol/l), mean (SD) (<i>n</i> = 568)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)
Triglycerides (mmol/l), mean (SD) (<i>n</i> = 568)	1.1 (0.6)	1.1 (0.7)	1.3 (1.3)
Stable glucose balance, % (<i>n</i> = 227)			
FPG < 5.0 mmol/l at 31 and 46 years (ref.)	43.7	44.3	53.8
FPG 5.0–5.59 mmol/l at 31 and 46 years	45.2	48.9	30.8
FPG 5.6–6.9 (prediabetes) at 31 and 46 years	11.1	6.8	15.4
Worsened glucose balance, % (<i>n</i> = 302)			
FPG < 5.0 mmol/l at 31 and 46 years (ref.)	35.0	30.5	41.2
FPG < 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years	47.8	57.0	41.2
FPG < 5.0 mmol/l at 31 and 5.6–6.9 (prediabetes) at 46 years	17.2	12.5	17.6

BMI, body mass index; HDL, high density lipoprotein; FPG, fasting plasma glucose.

Table 3a. Basic characteristics of the study population [proportions/means and their standard deviations (SD)] categorized according to the fasting plasma glucose levels at 31 and 46 years

	Reference category	Stable glucose balance		Worsened glucose balance	
	< 5.0 mmol/l at 31 and 46 years (<i>n</i> = 109)	5.0–5.59 mmol/l at 31 and 46 years (<i>n</i> = 119)	5.6–6.9 mmol/l (prediabetes) at 31 and 46 years (<i>n</i> = 24)	< 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years (<i>n</i> = 179)	< 5.0 mmol/l at 31 and 5.6–6.9 mmol/l (prediabetes) at 46 years (<i>n</i> = 56)
Gender, % (stable, <i>n</i> = 252)					
(worsened, <i>n</i> = 344)					
Male	14.7	47.9	79.2	33.3	54.5
Female	85.3	52.1	20.8	66.7	45.5
Education, % (stable, <i>n</i> = 243)					
(worsened, <i>n</i> = 337)					
Basic	21.7	28.3	50.0	25.8	24.5
Intermediate	50.9	54.0	45.8	52.8	45.3
Higher	27.4	17.7	4.2	21.3	30.2
Toothbrushing frequency, %					
(stable, <i>n</i> = 252)					
(worsened, <i>n</i> = 343)					
Twice a day or more	85.3	68.1	62.5	78.2	63.6
Once a day	14.7	31.9	37.5	52.7	34.5
Less frequently	0.0	0.0	0.0	0.0	1.8
Most recent dental visit, %					
(stable, <i>n</i> = 243)					
(worsened, <i>n</i> = 332)					
Less than 1 year ago	58.5	59.1	45.5	63.4	57.4
1–2 years ago	32.1	22.6	36.4	25.6	31.5

≥ 3 years ago	9.4	18.3	18.2	11.0	11.1
Frequency of physical exercise, %					
(stable, <i>n</i> = 248)					
(worsened, <i>n</i> = 340)					
2–3 times a month or less frequently	20.4	19.8	21.7	20.8	24.1
Once a week	17.6	24.8	21.7	17.4	18.5
2–3 times a week	43.5	41.0	34.8	43.3	40.7
Daily or 4–6 times a week	18.5	14.5	21.7	18.5	16.7
Alcohol consumption, %					
(stable, <i>n</i> = 252)					
(worsened, <i>n</i> = 344)					
0 g / day	18.3	14.3	8.3	8.9	7.3
0.001–3.0 g / day	40.4	40.3	45.8	38.3	32.7
> 3.0–11.1 g /day	32.1	24.4	25.0	36.7	29.1
> 11.1 g /day	9.2	21.0	20.8	16.1	30.9
BMI (kg/m²), %					
(stable, <i>n</i> = 252)					
(worsened, <i>n</i> = 344)					
< 24.9	68.8	47.9	33.3	45.0	16.4
25–29.9	25.7	34.5	45.8	39.4	50.9
≥ 30	5.5	17.6	20.8	15.6	32.7
Total cholesterol (mmol/l), mean (SD)					
(stable, <i>n</i> = 252)	5.3 (0.8)	5.3 (0.9)	5.2 (0.9)	5.3 (0.9)	5.3 (1.2)
(worsened, <i>n</i> = 344)					
HDL cholesterol (mmol/l), mean (SD)					
(stable, <i>n</i> = 252) (worsened, <i>n</i> = 344)	1.7 (0.3)	1.6 (0.4)	1.4 (0.5)	1.6 (0.4)	1.5 (0.4)
Triglycerides (mmol/l), mean (SD)					
(stable, <i>n</i> = 252) (worsened, <i>n</i> = 344)	0.9 (0.5)	1.1 (0.8)	1.4 (0.8)	1.1 (0.5)	1.3 (0.7)
Number of teeth, mean (SD)					
(stable, <i>n</i> = 251) (worsened, <i>n</i> = 344)	27.0 (1.5)	26.9 (1.5)	26.8 (1.5)	27.1 (1.4)	26.7 (1.5)
Number of teeth with plaque, mean (SD)					
(stable, <i>n</i> = 250) (worsened, <i>n</i> = 343)	5.0 (5.8)	6.4 (6.9)	6.9 (7.7)	5.4 (6.3)	5.6 (5.2)
BOP, % of sites (SD)					
(stable, <i>n</i> = 249) (worsened, <i>n</i> = 341)	24.2 (16.1)	27.1 (18.2)	24.9 (18.2)	24.3 (16.5)	28.7 (17.2)

Number of sites with PPD ≥ 4 mm, mean (SD) (stable, $n = 249$) (worsened, $n = 340$)	1.0 (2.3)	2.2 (5.0)	1.5 (2.7)	1.8 (5.9)	1.4 (3.1)
Number of sites BL ≥ 5 mm, mean (SD) (stable, $n = 227$) (worsened, $n = 302$)	0.9 (1.4)	0.9 (1.4)	0.8 (1.5)	0.9 (1.3)	0.9 (1.4)

FPG, fasting plasma glucose; BMI, body mass index; HDL, high density lipoprotein; BOP, bleeding on probing.

Table 3b. Basic characteristics of the study population [proportions/means and their standard deviations (SD)] categorized by the level of education and the fasting plasma glucose levels at 31 and 46 years

	Reference category	Stable glucose balance		Worsened glucose balance	
	< 5.0 mmol/l at 31 and 46 years (<i>n</i> = 109)	5.0–5.59 mmol/l at 31 and 46 years (<i>n</i> = 119)	5.6–6.9 mmol/l (prediabetes) at 31 and 46 years (<i>n</i> = 24)	< 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years (<i>n</i> = 179)	< 5.0 mmol/l at 31 and 5.6–6.9 mmol/l (prediabetes) at 46 years (<i>n</i> = 56)
Low education					
Gender, Male % (stable, <i>n</i> = 67) (worsened, <i>n</i> = 82)	17.4	65.6	83.3	43.5	53.8
Toothbrushing twice a day or more, % (stable, <i>n</i> = 67) (worsened, <i>n</i> = 82)	73.9	56.3	50.0	56.5	61.5
Most recent dental visit , ≥ 3 years ago, % (stable, <i>n</i> = 63) (worsened, <i>n</i> = 78)	4.5	30.0	18.2	13.6	25.0
Alcohol consumption g/ day, mean (SD) (stable, <i>n</i> = 67) (worsened, <i>n</i> = 80)	3.6 (5.1)	6.3 (7.6)	11.8 (20.6)	6.2 (9.9)	4.2 (4.0)
BMI (kg/m²) ≥ 30, % (stable, <i>n</i> = 67) (worsened, <i>n</i> = 82)	4.3	21.9	25.0	19.6	30.8
High education					
Gender, Male % (stable, <i>n</i> = 176) (worsened, <i>n</i> = 255)	13.3	43.2	75.0	30.3	55.0
Toothbrushing twice a day or more % (stable, <i>n</i> = 176) (worsened, <i>n</i> = 254)	90.4	71.6	75.0	85.5	65.0
Most recent dental visit , ≥ 3 years ago, % (stable, <i>n</i> = 171) (worsened, <i>n</i> = 248)	8.6	15.2	18.2	10.2	7.5
Alcohol consumption , g/ day, mean (SD)	3.4 (5.5)	5.4 (8.3)	6.4 (5.4)	5.6 (9.8)	11.7 (18.6)

(stable, $n = 170$) (worsened, $n = 247$)

BMI (kg/m²) ≥ 30 , %

6.0

14.8

16.7

14.4

32.5

(stable, $n = 176$) (worsened, $n = 255$)

FPG, fasting plasma glucose; BMI, body mass index.

Table 4. Associations of stable and worsened glucose balance with the numbers of sites with ≥ 4 mm probing pocket depths (PPD ≥ 4 mm) and alveolar bone loss (BL ≥ 5 mm) using Poisson regression models [relative risk (RR) with 95 % confidence intervals (95 % CI)] in the total population and in individuals with a high level of education. Only individuals with no missing data were included

	Total population		High education
	Unadjusted RR (95% CI)	Adjusted RR ¹ (95% CI)	Adjusted RR ² (95% CI)
	<i>n</i> = 647	<i>n</i> = 647	<i>n</i> = 448
Stable glucose balance			
The two-class FPG categorization (ADA):			
PPD ≥ 4 mm			
< 5.6 mmol/l at 31 and 46 years (ref.)	1	1	1
5.6–6.9 mmol/l (prediabetes) at 31 and 46 years	1.1 (0.8–1.5)	0.9 (0.6–1.2)	0.3 (0.1–0.6)
BL ≥ 5 mm			
< 5.6 mmol/l at 31 and 46 years (ref.)	1	1	1
5.6–6.9 mmol/l (prediabetes) at 31 and 46 years	1.2 (0.7–1.9)	1.1 (0.7–1.7)	1.0 (0.5–1.8)
The three-class FPG categorization:			
PPD ≥ 4 mm			
< 5.0 mmol/l at 31 and 46 years (ref.)	1	1	1
5.0–5.59 mmol/l at 31 and 46 years	2.5 (2.0–3.1)	1.7 (1.3–2.2)	3.3 (2.4–4.5)
5.6–6.9 mmol/l (prediabetes) at 31 and 46 years	1.9 (1.3–2.8)	1.1 (0.7–1.6)	0.7 (0.3–1.5)
BL ≥ 5 mm			
< 5.0 mmol/l at 31 and 46 years (ref.)	1	1	1
5.0–5.59 mmol/l at 31 and 46 years	1.0 (0.8–1.3)	0.9 (0.6–1.3)	1.1 (0.7–1.6)
5.6–6.9 mmol/l (prediabetes) at 31 and 46 years	1.2 (0.7–2.0)	0.9 (0.5–1.6)	1.0 (0.5–2.1)
Worsened glucose balance			
The two-class FPG categorization (ADA):			

PPD ≥ 4 mm			
< 5.6 mmol/l at 31 and 46 years (ref.)	1	1	1
< 5.6 mmol/l at 31 and 5.6 – 6.9 mmol/l (prediabetes) at 46 years	1.0 (0.9–1.2)	1.0 (0.8–1.1)	0.9 (0.7–1.1)
BL ≥ 5 mm			
< 5.6 mmol/l at 31 and 46 years (ref.)	1	1	1
< 5.6 mmol/l at 31 and 5.6 – 6.9 mmol/l (prediabetes) at 46 years	1.2 (0.9–1.4)	1.3 (1.0–1.6)	0.9 (0.6–1.2)
The three-class FPG categorization:			
PPD ≥ 4 mm			
< 5.0 mmol/l at 31 and 46 years (ref.)	1	1	1
< 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years	1.8 (1.4–2.2)	1.8 (1.4–2.2)	1.3 (0.9–1.7)
< 5.0 mmol/l at 31 and 5.6 – 6.9 mmol/l (prediabetes) at 46 years	1.9 (1.4–2.5)	2.8 (2.0–3.8)	0.8 (0.5–1.3)
BL ≥ 5 mm			
< 5.0 mmol/l at 31 and 46 years (ref.)	1	1	1
< 5.0 mmol/l at 31 and 5.0–5.59 mmol/l at 46 years	1.0 (0.8–1.3)	1.1 (0.8–1.4)	1.2 (0.8–1.6)
< 5.0 mmol/l at 31 and 5.6 – 6.9 mmol/l (prediabetes) at 46 years	1.5 (1.1–2.2)	1.8 (1.2–2.8)	1.4 (0.8–2.3)

¹ Adjusted for gender, BMI, education, number of teeth with plaque, and number of tooth sites (offset).

² Adjusted for gender, BMI, number of teeth with plaque, and number of tooth sites (offset).