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Original article

Does periodontitis affect diabetes incidence and haemoglobin A1c change? An 11-year follow-up study

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ABSTRACT

Aim. – As periodontitis may contribute to the pathogenesis of diabetes, the effects of periodontitis on diabetes incidence and HbA1c change was quantified in a prospective cohort.
Methods. – Data from an 11-year follow-up of the Study of Health in Pomerania were analyzed to evaluate the effects of periodontitis on incident diabetes and long-term HbA1c changes in 2047 subjects aged 20–81 years. Diabetes was based on self-reported physician diagnoses, antidiabetic medication use, or HbA1c $\geq$ 6.5% or non-fasting blood glucose levels $\geq$ 11.1 mmol/L. To assess periodontal status, periodontal pockets were probed, and their depth and clinical attachment levels measured. For both measures, means and percentages of sites $\geq$ 3 mm were calculated. In addition, all probing depths $\geq$ 4 mm were summed (cumulative probing depth). Modified Poisson and multivariable linear models were applied, adjusted for age, gender, highest level of general education, marital status, waist circumference, physical activity, smoking status and follow-up time.
Results. – Over a mean follow-up period of 11.1 years, 207 subjects developed diabetes. Baseline mean clinical attachment levels (CAL) and probing depths (PPD) were not significantly associated with either diabetes incidence [mean CALs, fourth quartile, incidence rate ratio = 0.819, 95% confidence interval (CI): 0.489–1.370; $P = 0.446$] or long-term changes in HbA1c (mean CAL, fourth quartile, $\beta = -0.086$, 95% CI: −0.187, −0.016; $P = 0.098$). Sensitivity analyses using alternative exposure definitions confirmed these results.
Conclusion. – Contrary to the currently available literature, no convincing evidence was found of any potential association between periodontitis and diabetes incidence or HbA1c change.

Introduction

Diabetes mellitus represents a major global health burden. Approximately 415 million people worldwide live with diabetes, and this number is expected to increase to 642 million by 2040 [1]. Over the next few decades, the prevalence of diabetes is likely to increase in the developed and especially the developing countries [2]. For this reason, examining other clinical conditions that may predispose to diabetes could have important public-health implications for early diabetes care and management.

Periodontitis is characterized by chronic infection and inflammation of tooth-supporting tissues [3]. Periodontal infection may cause systemic inflammation [4] via low-grade, continuous bacteraemia or by spillover of proinflammatory cytokines locally produced in the gingiva into the bloodstream [5,6]. In turn, advanced glycation end-products (AGEs) are produced [7], which

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contribute to the onset of diabetes via increased dysregulation of metabolic control [8].

In recent years, the bidirectional association between diabetes and chronic periodontitis has received considerable attention [9,10]. However, longitudinal epidemiological data describing the effects of periodontitis on the development of diabetes in the general population are scarce and have contributed to the current evidence only to a limited degree [11–14]. In the adult US population (aged 25–74; $n = 9296$), examined in the first National Health and Nutrition Examination Survey (NHANES), performed in the early 1970s, individuals with higher periodontal index categories exhibited greater odds of developing future diabetes [13]. On analyzing data from 2973 diabetes-free subjects in the Study of Health in Pomerania (SHIP) [15], participants in the highest periodontal disease category (as defined by quartiles (Q) of the percentage of sites with clinical attachment levels [CAL] ≥ 5 mm) had a 0.08% higher 5-year haemoglobin A1c (HbA1c) change compared with participants in the lowest periodontal disease category. In an Asian retrospective cohort study ($n = 22{,}299$), those with periodontitis, as indicated by a need for surgery, exhibited a 1.19-fold higher incidence of diabetes than those without periodontitis matched from the general population [11]. Another study of 2469 male Japanese workers [12] revealed an increased relative risk [risk ratio (RR): 1.73] for incident type 2 diabetes (T2D) in those reporting tooth loss. In contrast, another study reported a non-significant association between moderate or severe periodontitis (using scores 3–4 of the Community Periodontal Index) and incident diabetes in a large ($n = 5848$) prospective 7-year follow-up study of Japanese adults [14]. While most of these studies were large-scale, they had serious limitations in terms of study design, exposure/outcome assessment and/or insufficient confounder adjustment, thereby limiting their contribution to the current evidence.

At present, there is no consensus on the case definition of chronic periodontitis [16,17]. Thus, exposure/outcome effects were estimated using definitions favourable from an epidemiological and statistical point of view. Periodontal disease status is commonly assessed by current (pocket probing depth, PPD) and cumulative (CAL) disease measures. Using both measures, our present study evaluated the different definitions quantifying disease severity (mean) and extent (percentage of diseased sites) [18,19]. In addition, the cumulative PPD, which quantifies current periodontal inflammation and is sensitive to reductions in inflammatory exposure, was also determined [20]. Exposure definitions were analyzed continuously, thereby reducing the chances of misclassification, and as quartiles. By using various exposure definitions and parameters, the constancy of the potential exposure/outcome effects was thoroughly evaluated, thus strengthening the validity of our conclusions.

In light of the above facts, the effects of various baseline periodontitis definitions on incident diabetes in 2047 diabetes-free individuals were also examined using prospective data from the population-based SHIP-0 and SHIP-2. In addition, the effects of periodontitis definitions on long-term changes in HbA1c levels were also assessed.

Methods

Study population

The SHIP is an ongoing longitudinal population-based health survey in West Pomerania [21]. A two-stage cluster sampling method was adopted from the World Health Organization (WHO) Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project based in Augsburg, Germany [22]. Caucasian subjects of both genders with German citizenship and main residency in the study area were randomly sampled within 12 5-year age strata, each including 292 subjects. The remaining net sample (excluding the emigrated and deceased) comprised 6265 eligible subjects. In the end, 4308 subjects participated in the baseline examinations between 1997 and 2001 (SHIP-0). Of these, 3300 subjects participated in the 5-year SHIP-1 follow-up examinations during 2002–2006. Of the 3708 eligible individuals who participated in SHIP-0 and were also invited to participate in the 11-year follow-up, 2333 were ultimately examined between 2008 and 2012 (SHIP-2; 62.9% follow-up response) [23].

The study protocol was approved *a priori* by the Ethics Committee of the University of Greifswald, and written informed consent was obtained from each participant. This study was performed in accordance with "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" guidelines for human research studies [24].

Detailed information on the non-responses, exclusion criteria, and number and type of missing data is presented in Fig. S1 (see supplementary material associated with this article online). Of the 2333 subjects who completed the follow-up, 145 participants with prevalent diabetes at baseline were excluded. Information on diabetes status and HbA1c measurements were not recorded for a further 124 participants, and data on mean PPD and edentulism at baseline were not available for 18 individuals. In addition, 12 subjects were missing covariate information, leaving 2034 participants for the final analyses. For analyses of HbA1c changes from baseline, the relevant sample comprised 1932 subjects after exclusion of 102 subjects taking antidiabetic medication.

Periodontitis assessment

Licensed calibrated dentists (eight in SHIP-0, six in SHIP-2) performed the oral examinations. The periodontal recording protocols in SHIP-0 and SHIP-2 were identical. Periodontal measurements were assessed at four sites (distobuccal, mesiobuccal, midbuccal, midlingual/midpalatinal) per tooth according to the half-mouth method, alternating on the left or right side and excluding third molars. A periodontal probe (PCP11, Hu-Friedy Mfg. Co., LLC, Chicago, IL, USA) was used to assess PPD and CAL. PPD was measured as the distance between the free gingival margin and pocket base, while CAL was the distance between the cementoenamel junction (CEJ) and pocket base. If the CEJ was visible, then CAL and PPD were measured directly; otherwise, the distance between the gingival margin and CEJ was subtracted from the PPD to calculate the CAL. Where the CEJ was indistinct (due to, for example, wedge-shaped defects, fillings, crown margins), CAL was not recorded. Measurements were mathematically rounded to the nearest mm. The number of teeth present was counted, excluding third molars.

Calibration exercises were performed during the course of both studies. Dentists were trained a priori by the same periodontist (T.K.). For CAL, interclass correlations were 0.84 in SHIP-0 and 0.74 in SHIP-2, whereas intraclass correlations per examiner were 0.82–0.91 in SHIP-0 and 0.76–0.88 in SHIP-2 [25,26].

To assess periodontitis status, PPD was defined as the primary measure. The mean PPD [19], percentage of sites with PPD ≥ 3 mm [18,19] and cumulative PPD [sum of the deepest PPDs (≥ 4 mm) per tooth] [20] were calculated on the individual level and categorized as either Q1–Q4 or analyzed continuously. CAL was defined as the secondary exposure measure. The mean CAL and percentage of sites with CAL ≥ 3 mm [18,19] were calculated on the subject level and categorized as either Q1–Q4 or analyzed continuously. If PPD and CAL definitions were analyzed as Q1–Q4, then edentulous subjects were considered an additional

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