

Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial

Francesco D'Aiuto, Nikolaos Gkraniias, Devina Bhowruth, Tauseef Khan, Marco Orland, Jean Suvan, Stefano Masi, Georgios Tsakos, Steve Hurel, Aroon D Hingorani, Nikos Donos*, John E Deanfield*, for the TASTE Group

Summary

Background Chronic inflammation is believed to be a major mechanism underlying the pathophysiology of type 2 diabetes. Periodontitis is a cause of systemic inflammation. We aimed to assess the effects of periodontal treatment on glycaemic control in people with type 2 diabetes.

Methods In this 12 month, single-centre, parallel-group, investigator-masked, randomised trial, we recruited patients with type 2 diabetes, moderate-to-severe periodontitis, and at least 15 teeth from four local hospitals and 15 medical or dental practices in the UK. We randomly assigned patients (1:1) using a computer-generated table to receive intensive periodontal treatment (IPT; whole mouth subgingival scaling, surgical periodontal therapy [if the participants showed good oral hygiene practice; otherwise dental cleaning again], and supportive periodontal therapy every 3 months until completion of the study) or control periodontal treatment (CPT; supra-gingival scaling and polishing at the same timepoints as in the IPT group). Treatment allocation included a process of minimisation in terms of diabetes onset, smoking status, sex, and periodontitis severity. Allocation to treatment was concealed in an opaque envelope and revealed to the clinician on the day of first treatment. With the exception of dental staff who performed the treatment and clinical examinations, all study investigators were masked to group allocation. The primary outcome was between-group difference in HbA_{1c} at 12 months in the intention-to-treat population. This study is registered with the ISRCTN registry, number ISRCTN83229304.

Findings Between Oct 1, 2008, and Oct 31, 2012, we randomly assigned 264 patients to IPT (n=133) or CPT (n=131), all of whom were included in the intention-to-treat population. At baseline, mean HbA_{1c} was 8.1% (SD 1.7) in both groups. After 12 months, unadjusted mean HbA_{1c} was 8.3% (SE 0.2) in the CPT group and 7.8% (0.2) in the IPT group; with adjustment for baseline HbA_{1c}, age, sex, ethnicity, smoking status, duration of diabetes, and BMI, HbA_{1c} was 0.6% (95% CI 0.3-0.9; p<0.0001) lower in the IPT group than in the CPT group. At least one adverse event was reported in 30 (23%) of 133 patients in the IPT group and 23 (18%) of 131 patients in the CPT group. Serious adverse events were reported in 11 (8%) patients in the IPT group, including one (1%) death, and 11 (8%) patients in the CPT group, including three (2%) deaths.

Interpretation Compared with CPT, IPT reduced HbA_{1c} in patients with type 2 diabetes and moderate-to-severe periodontitis after 12 months. These results suggest that routine oral health assessment and treatment of periodontitis could be important for effective management of type 2 diabetes.

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Introduction

The worldwide epidemic of type 2 diabetes is a major cause of disability and premature mortality, mainly from vascular and renal complications.¹ Inflammation can affect glycaemic control in patients with diabetes and is implicated in atherosclerosis and chronic kidney disease.² However, whether effective control of systemic inflammation can improve glycaemic control in people with type 2 diabetes and thereby reduce their risk of diabetes complications remains unclear.

Periodontitis is a chronic inflammatory disease, which often coexists with diabetes.³ It is caused by a dysbiosis of the oral microbiota and is associated with a dysregulated

immune-inflammatory response.⁴ The response induced by accumulation of bacteria on the tooth surface is not only confined to the oral cavity, but is also associated with systemic inflammation.⁵ The elevated systemic inflammatory burden in people with periodontitis has been associated with increased risk of chronic and potentially life-threatening diseases including diabetes, cardiovascular disease, and end-stage renal failure.⁶

Periodontal therapy is usually delivered over three phases: an initial phase, a corrective phase, and a final supportive phase. During the initial phase, any essential dental care, oral hygiene advice, and teeth cleaning (scaling of the teeth, including subgingival root debridement) are

* Contributed equally

† Members are listed in the appendix

Periodontology Unit, UCL Eastman Dental Institute and Hospital (Prof F D'Aiuto PhD, M Orlandi PhD, J Suvan PhD), Department of Epidemiology and Public Health (G Tsakos PhD), Department of Endocrinology, University College London Hospitals (S Hurel PhD), and Institute of Cardiovascular Sciences (D Bhowruth CVS, T Khan PhD, S Masi MD, Prof A D Hingorani PhD, Prof J E Deanfield MB), University College London, London, UK; and Centre for Clinical Oral Research, Institute of Dentistry, Barts & The London School of Medicine and Dentistry, Queen Mary University of London, London, UK (N Gkraniias PhD, N Donos PhD)

Correspondence to: Prof Francesco D'Aiuto, UCL Eastman Dental Institute, University College London, London WC1X 8LD, UK
f.daiuto@ud.ac.uk

Research in context

Evidence before this study

To identify intervention trials and systematic reviews on the effects of periodontal treatment on metabolic control in patients with type 2 diabetes published before the start of this trial, we searched PubMed for reports published in English between database inception and Dec 31, 2006. We used the following search terms: "diabetes", "periodontal", "periodontitis", "treatment", "clinical trial", "systematic review", and "meta-analysis". Pooled estimates from meta-analyses of small intervention trials showed a slight improvement in metabolic control after non-surgical periodontal treatment (HbA_{1c} reduced by around 0.3–0.4 percentage points compared with control periodontal therapy). Large heterogeneity among clinical trials was a major limitation due to inclusion of trials including patients with type 1 and type 2 diabetes, variable follow-up times (up to 6 months), and different treatment modalities. Small sample sizes were also a limitation in these earlier studies.

Added value of this study

Our aim was to show whether effective periodontal treatment would affect metabolic status in patients with type 2 diabetes. On the basis of the high risk for cardiovascular and renal complications reported in patients with type 2 diabetes, we also investigated the effect of periodontal treatment on

vascular and renal functions. This is the first study to show that periodontal treatment improves metabolic control (reducing HbA_{1c} and plasma glucose concentrations) and vascular and kidney functions, reduces systemic inflammation, and improves quality of life in patients with type 2 diabetes after 12 months.

Implications of all the available evidence

A 2015 Cochrane systematic review concluded that non-surgical periodontal therapy has short-term effects on metabolic control in patients with type 2 diabetes, but noted that longer controlled clinical trials were needed to confirm long-term effects. The Cochrane review included three studies with small sample sizes that had 12 months follow-up after periodontal therapy, the results of which suggested a positive effect on metabolic control. Our study shows that periodontal treatment has beneficial effects on metabolic control in patients with type 2 diabetes over 12 months. Our results suggest a causal relation between periodontitis and control of diabetes and its key complications. Oral health promotion in patients with type 2 diabetes is a novel and potentially beneficial therapeutic opportunity. Diabetes care providers should discuss the importance of oral health with their patients and consider incorporating routine dental assessment and treatment into lifelong preventive programmes.

done. At least 8 weeks after the dental cleaning sessions, a re-evaluation of the periodontal condition is done, together with an assessment of the patient's self-performed oral hygiene. The corrective phase of therapy includes additional surgical periodontal therapy (if oral hygiene is optimum) or a repetition of the scaling and root debridement (if oral hygiene is suboptimum). This second phase is usually completed within 1–2 months; therefore, at around 3 months after the final periodontal surgical session, a reassessment is done to enable selection of the third phase of therapy—the phase. This final phase is an open-ended protocol of sessions, usually every 3 months, that includes oral hygiene advice and professional non-surgical dental cleaning as required.

We have previously shown that treatment of periodontitis results in substantial reduction of systemic inflammatory markers and improved conduit artery endothelial function at 6 months, which is regarded as an early indicator of atherosclerosis.⁷ Previous studies have investigated the effect of periodontitis treatment on short-term (2–6 months' follow-up) glycaemic control in patients with diabetes, with significant reductions of HbA_{1c}, of 0.3–0.4 percentage points being reported.⁸ However, these studies often had low numbers of participants and included a mixture of patients with type 1 and 2 diabetes; some studies were done with adjuvant local or systemic antimicrobial

drugs.⁹ Furthermore, the ineffectiveness of non-surgical periodontal therapy in patients with diabetes has been debated as one of the major confounders of the association between the two disorders. The potential benefits of periodontitis treatment on diabetes complications therefore remain unknown.

Our group previously showed that intensive periodontal therapy was needed to observe a systemic benefit.¹ We hypothesised that effective treatment of periodontitis, in which local and systemic inflammation are reduced, would improve glycaemic control in patients with type 2 diabetes, thereby enhancing vascular and renal function and quality of life.

Methods

Study design and participants

We did a 12 month, single-centre, parallel-group, investigator-masked, randomised trial to assess the effect of intensive periodontal therapy (non-surgical and surgical) compared with usual care (the care provided at regular dental check-ups—namely, cleaning and polishing the part of the tooth that is visible above the gingiva). We enrolled consecutive patients into the study if they had type 2 diabetes (using WHO diagnostic criteria) for

6 months or longer,¹⁰ moderate-to-severe periodontitis (>20 periodontal pockets with probing pocket depths of >4 mm and marginal alveolar bone loss of >30%), and at

so that eligible participants would present with active signs of gingival inflammation rather than history of breakdown of periodontal soft and hard tissues. We recruited eligible participants from among referrals to the Eastman Dental Hospital (Periodontology Unit), University College Hospital (outpatients of the Department of Endocrinology), and Ealing and St Mary's Hospitals in London, UK. Patients were additionally recruited from 15 general medical or dental practices in the Greater London area (identified using registration data from the Diabetes Research Network). Exclusion criteria were uncontrolled systemic diseases other than diabetes (cardiovascular diseases [including hypertension], liver diseases, pulmonary diseases, end-stage renal failure, or neoplasm); hepatitis B or HIV infection; chronic treatment (>2 weeks) with drugs known to affect periodontal tissues (phenytoin or ciclosporin); chronic systemic antibiotic treatment; and pregnancy or lactation. All participants provided written informed consent. The study was approved by the joint University College London/University College London Hospital Committees on Ethics of Human Research (Committee A) in November, 2007 (Ref07fH0714j97). The original protocol was amended and re-approved by the same committee in July, 2008, April, 2010, and June, 2010.

A steering committee group met every 3 months to monitor study progress. The results of this meeting were communicated with an independent safety monitoring group, which reviewed any progression of periodontitis throughout the trial. No interim analyses were planned.

Randomisation and masking

We randomly assigned patients (1:1) using a computer-generated table to receive intensive periodontal treatment (IPT) or control periodontal treatment (CPT). Treatment allocation included a process of minimisation,¹¹ taking account of diabetes duration, smoking status, sex, and severity of periodontitis. Allocation to treatment was concealed in an opaque envelope and revealed to the clinician and patient on the day of first treatment. With the exception of the study dental staff delivering the treatment and performing the clinical examinations, all other investigators (vascular examiner, nurses collecting anthropometric measures and blood samples, laboratory staff who analysed the serum samples, staff involved with the data collection and analyses, and report authors) were masked to the group allocation.

Procedures

Essential dental care, including oral hygiene instructions and removal of compromised teeth, was done in both IPT and CPT groups (appendix). Teeth were extracted if they were deemed unsalvageable: ie, if their prognosis was very poor despite restorative efforts, the surrounding jaw bone was lost in close proximity to the tip of the root of the tooth (apex), the teeth were mobile (grade III), or there was a radiographic translucency around the root tip (possibly on a tooth that had undergone previous root canal treatment),

which indicates unhealed jaw bone and possible abscess and pus flow.

Patients in the IPT group received an initial single session of whole mouth scaling of the root surfaces under local analgesia, with no time limit set for the duration of the session. 2 months after the first whole mouth scaling session, patients with good oral hygiene (dental plaque scores of <20%) and at least one 6 mm or deeper residual periodontal pocket had periodontal surgical therapy to improve access for root surface debridement. Patients who still had suboptimal oral hygiene or did not have residual 6 mm or deeper periodontal pockets at 2 months received additional scaling of the root surfaces under local analgesia. All patients in the IPT group subsequently received further sessions of scaling of the root surfaces under local analgesia every 3 months until completion of the study.

Patients in the CPT group received supra-gingival scaling and polishing of all dentition at the same time-points as the IPT group (after baseline and at 2, 6, 9, and 12 months after the completion of the first session of periodontal therapy). At the end of the study, patients in the CPT group received any additional periodontal therapy that was required. Patients who showed progression of periodontitis at any point received prompt specialist care and were withdrawn from the study.

Patients were allocated to clinicians in a random order using a computer-generated sequence to minimise treatment bias. Diabetes treatment was managed by the local endocrinology consultant and nurses using standard clinical guidelines in both groups, and diabetes clinicians were unaware of group assignment throughout the study. Patients were asked not to discuss their study group allocation with diabetes care professionals or the other study investigators. Only the treatment clinician discussed details of the assigned treatment with the patient. The clinical team delivering periodontal therapy in both groups included two dental hygienists, two dentists, and three periodontists (appendix). Two trained and calibrated examiners collected medical and dental histories at baseline, and measured periodontal and clinical parameters at baseline and at each study visit, as previously described.⁷ Periodontal parameters included gingival probing depth and recession of the gingival margin relative to the cemento-enamel junction at six sites per tooth; presence or absence of supra-gingival dental plaque and gingival bleeding on probing; averaged whole mouth number of periodontal lesions (probing depth of >4 mm); and relative percentages of presence of gingival bleeding (full mouth gingival bleeding scores [number of sites with gingival bleeding on probing/total number of sites per mouth x 100]) and supra-gingival dental plaque (full mouth plaque scores [number of sites with visible detectable plaque/total number of sites per mouth x 100]). Clinical parameters included tobacco exposure (current, former, or never smoker), blood pressure, height, bodyweight, waist circumference, and body-fat mass (data not reported).

Medication use was collected at baseline by detailed interview and prescription assessment and reviewed at study visits using a detailed medication log. Semi-quantitative food frequency questionnaires (detailed analyses taking into account the basal metabolic rate are to be reported elsewhere); self-reported data on general health (data not presented); and questionnaires to assess diabetes-related quality of life (Audit of Diabetes Dependent Quality of Life), oral health (Oral Impacts on Daily Performance), and oral health-related quality of life (data not presented) were administered at baseline and at 12 months. Examiner calibration exercises were repeated every 6 months for the duration of the study.

Fasting blood samples were collected at baseline and at study visits. Samples were centrifuged and stored within 1 h of collection. All plasma aliquots were stored at -70°C for analysis at the end of the study. HbA_{1c} was measured using liquid chromatography. Concentrations of glucose, standard lipid fractions (total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides), and insulin were measured using standard assays and an automated analyser (Cobas 8000 analyser, Roche, Mannheim, Germany). Homeostasis Model Assessment (HOMA2) scores were calculated. Serum C-reactive protein (CRP) concentrations were determined by immunoturbidimetry (Cobas Integra 700, Roche, Mannheim, Germany). Full blood differential count was assessed using standard biochemical tests in real time on the day of collection. The remaining assays were performed on stored samples at the end of the study. Inflammatory

biomarkers (interleukin 1p, interleukin 6, interleukin 8, interleukin 10, interleukin 12, interferon γ , and tumour necrosis factor α [TNF α]) and endothelial cell surface markers (E-selectin, P-selectin, intercellular adhesion molecule 3, and thrombomodulin) were measured by multiplex assay (Meso Scale Discovery, Rockville, MD, USA; interassay and intra-assay coefficients of variation $<7\%$). Serum creatinine was measured on an automated analyser (Cobas 8000). Estimated glomerular filtration rate (eGFR) was calculated using the four-variable Modification in Diet in Renal Disease equation."

Endothelium-dependent and endothelium-independent flow-mediated dilatation (FMD) was assessed by ultrasound imaging of the brachial artery with a high resolution probe (7 MHz), as previously described.¹⁶ 10 year coronary heart disease and stroke risk scores were calculated at baseline and at 12 months using the UK Prospective Diabetes Study (UKPDS) Risk Engine.

Outcomes

The prespecified primary outcome was the difference in HbA_{1c} between the IPT and CPT groups at 12 months. Prespecified secondary endpoints reported here were differences between groups in HbA_{1c} at 6 months; glucose, insulin, and creatinine concentrations and FMD at 6 and 12 months; adverse events reported at study visits (defined as any changes in anatomical, physiological, or metabolic functions occurring in any phase of the clinical study, whether or not associated with the study); periodontal clinical parameters, lipid fractions, and inflammatory and endothelial cell surface markers at 2, 6, and 12 months; and eGFR and patient-reported outcomes at 12 months, including overall caloric intake and quality of life (Audit of Diabetes Dependent Quality of Life scores). Prespecified secondary outcomes to be reported elsewhere were between-group differences in dental plaque composition, laser Doppler flowmetry, intima-media thickness, and endothelium pulse amplitude tonometry.

We did post-hoc analyses of the following endpoints: between-group differences in HOMA2 scores at baseline and at 6 and 12 months after therapy; between-group differences in 10 year cardiovascular risk scores at baseline and at 12 months; between-group differences in change in diabetes medications (including dose increase and decrease) and systemic antibiotic use from each study visit to the next; and whole-group correlation analyses between metabolic, inflammatory, kidney, and periodontal parameters at 6 and 12 months.

Statistical analysis

We calculated that a minimum sample size of 129 participants per group was needed to detect a difference in HbA_{1c} of 1 percentage point (SD 2.1) at 12 months between groups, with an α of 0.05 and 95% power (assuming a 10% loss to follow-up).

Data are reported as mean and SD, unless otherwise specified. We did all analyses in the intention-to-treat

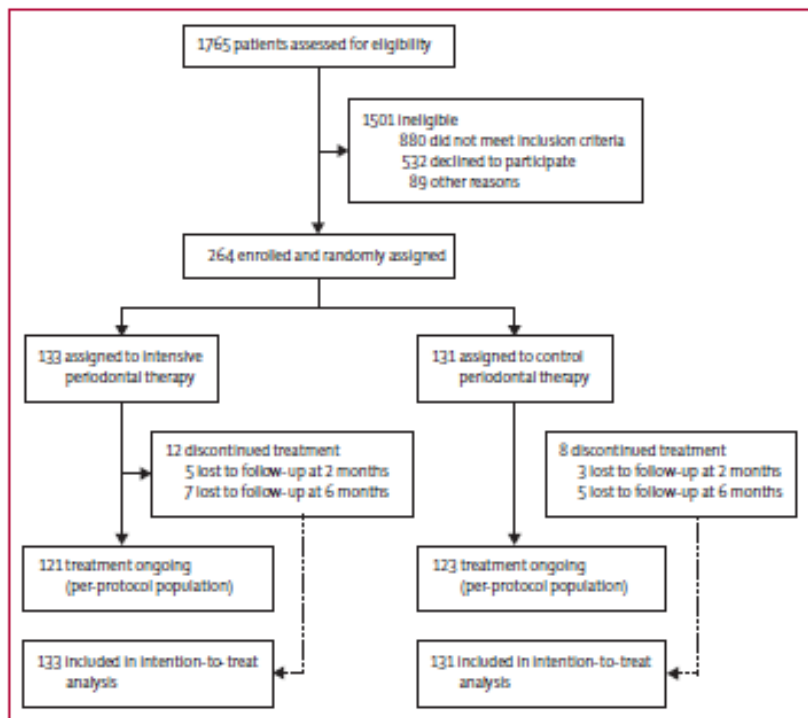


Figure 7: Trial profile

population and used the last measure carried forward approach for missing values. We repeated the analyses of all primary and secondary outcomes using post-hoc missing-value analyses with linear digital interpolation. A per-protocol population was defined as all participants in the intention-to-treat population who had at least one assessment of efficacy deemed to be unaffected by protocol violations. We did per-protocol analyses for all outcomes; the estimates derived from these analyses are reported for the primary outcome (HbA_{1c}) and any secondary or post-hoc outcomes if they differed from estimates obtained in the intention-to-treat population.

We modelled the primary and secondary outcomes using multilevel linear regression with the xtmixed command in Stata (version 13; StataCorp, College Station, TX, USA).¹⁷ The models included the respective baseline measurement, treatment group (represented by one

dummy variable), stage of study visit (ie, at baseline, 2 months [if included], 6 months, and 12 months), and a treatment time interaction term as explanatory variables (covariates). Additional covariates included age, sex, ethnicity, smoking status, duration of diabetes, and BMI. We applied a multilevel model with random intercepts, which included logarithmic transformation of the data where appropriate, to all continuous biomarker outcomes (secondary outcomes). A model with random intercepts and unstructured variance-covariance was used because of the reduced SEs of within-participant and between-participant variance to all secondary outcomes. We did not adjust for multiple comparisons. Differences between study groups for primary and secondary outcomes at all study follow-up points (2, 6, and 12 months) were adjusted for respective baseline values, whereas the absolute values for each treatment group at a given timepoint were not.

| | Intensive periodontal therapy (n=133) | Control periodontal therapy (n=131) |
|--|---------------------------------------|-------------------------------------|
| Age (years) | 58.2 (9.7) | 55.5 (10.0) |
| Sex | | |
| Male | 82 (62%) | 83 (63%) |
| Female | 51 (38%) | 48 (37%) |
| Ethnicity | | |
| White | 43 (32%) | 52 (40%) |
| Asian | 54 (41%) | 43 (33%) |
| African | 25 (19%) | 34 (26%) |
| Other | 11 (8%) | 2 (2%) |
| Smoking history | | |
| Never | 75 (56%) | 70 (53%) |
| Current | 18 (14%) | 19 (15%) |
| Former | 40 (30%) | 42 (32%) |
| Family history of cardiovascular diseases* | | |
| Positive | 60 (45%) | 61 (47%) |
| Negative | 73 (55%) | 70 (53%) |
| Diabetes duration (years) | 8.3 (7.4) | 8.7 (8.4) |
| BMI (kg/m ²) | 30 (5) | 31 (6) |
| Waist circumference (cm) | 104 (13) | 103 (14) |
| Systolic blood pressure (mm Hg) | 135 (16) | 136 (17) |
| Diastolic blood pressure (mm Hg) | 82 (10) | 83 (9) |
| Flow-mediated dilatation | 3.9% (2.5) | 3.9% (2.5) |
| HbA _{1c} (%) | 8.8 (1.7) | 8.8 (1.7) |
| HbA _{1c} (mmol/mol) | 64.6 (19.1) | 65.4 (18.8) |
| Fasting glucose (mmol/L) | 7.8 (6.5-9.8) | 7.8 (6.3-9.7) |
| Fasting insulin (mIU/L) | 12.8 (7.3-20.4) | 11.8 (8.0-) |
| 1.9-3) HOMA2-cell function | 21.23 (34-13) | 19.82 (18-12) |
| HOMA2 insulin sensitivity | 558.15 (848.23) | 585.98 (904.24) |
| HOMA2 insulin resistance | 0.37 (0.48) | 0.38 (0.57) |
| Insulin use at baseline | 32 (24%) | 32 (24%) |
| Insulin daily dose at baseline (IU) | 52 (37) | 61 (42) |
| Total cholesterol (mmol/L) | 4.2 (1.0) | 4.3 (1.1) |

(Table continues in next column)

| | Intensive periodontal therapy (n=133) | Control periodontal therapy (n=131) |
|---|---------------------------------------|-------------------------------------|
| (Continued from previous column) | | |
| Triglycerides (mmol/L) | 1.6 (1.2) | 1.6 (1.1) |
| LDL cholesterol (mmol/L) | 2.2 (0.9) | 2.4 (0.9) |
| HDL cholesterol (mmol/L) | 1.2 (0.4) | 1.3 (0.4) |
| Creatinine serum (μmol/L) | 81.2 (19.4) | 80.9 (22.9) |
| eGFR (ml/min per 1.73 m ²) | 91.0 (22.4) | 90.4 (22.5) |
| UKPDS 10-year cardiovascular disease risk | 14.3% (14.5) | 15.5% (14.2) |
| C-reactive protein (mg/L) | 1.50 (0.90-3.80) | 1.80 (0.80-3.50) |
| Interferon γ (pg/ml) | 2.3 (2.7) | 3.5 (13.5) |
| Interleukin 10 (pg/ml) | 6.8 (4.3) | 6.9 (5.3) |
| Interleukin 12 (pg/ml) | 2.0 (7.1) | 7.5 (54.2) |
| Interleukin 6 (pg/ml) | 2.0 (1.7) | 2.3 (2.0) |
| Interleukin 8 (pg/ml) | 15.4 (9.9) | 17.0 (12.2) |
| E-selectin (pg/ml) | 42.0 (34.0) | 45.1 (39.0) |
| P-selectin (pg/ml) | 136.9 (66.3) | 139.7 (65.4) |
| siCAM3 (pg/mL) | 6.2 (8.4) | 6.0 (7.9) |
| Thrombomodulin (pg/ml) | 12.9 (13.9) | 13.4 (14.9) |
| Whole mouth plaque scores | 74% (18) | 75% (18) |
| Whole mouth bleeding scores | 65% (18) | 65% (21) |
| Mean periodontal probing depth (mm) | 3.9 (0.7) | 3.9 (0.8) |
| Number of periodontal pockets >4mm | 50 (22) | 55 (27) |
| Percentage of periodontal pockets >4 mm | 34% (16) | 35% (16) |
| Number of periodontal pockets >6 mm | 2.6 (24) | 2.4 (19) |
| Number of teeth | 2.6 (4) | 2.6 (4) |

Data are mean (SD), n (%), or median (IQR). HOMA2=Homeostasis Model Assessment 2. eGFR=estimated glomerular filtration rate. UKPDS=UK Prospective Diabetes Study. siCAM3=soluble intercellular adhesion molecule-3. +Heart attack, stroke, or hypertension

Table J: Baseline characteristics of the intention-to-treat population

We did Spearman-rank correlation analyses of differences in all primary and secondary outcomes.

We did a post-hoc sensitivity analysis for the primary outcome in subgroups based on use of medications other than glucose-lowering drugs. We also did a post-hoc subgroup analysis by periodontal treatment subgroup (defined as IPT with non-surgical and surgical treatment, IPT with non-surgical treatment, and CPT) assessing the differences between each treatment subgroup in HbA_{1c}, CRP and TNF α concentrations, and clinical periodontal parameters at the 12 month visit. Lastly, we determined the proportions of patients in each study group who achieved either a reduction in HbA_{1c} of at least 0.4 percentage points or a reduction of at least 0.9 percentage points at 12 months (χ^2 comparison).

For all analyses, a two-sided p value of less than 0.05 was regarded as significant.

This study was retrospectively registered on the ISRCTN registry, number ISRCTN83229304, on June 18, 2010, and amended on May 26, 2017.

Role of the funding source

The funder of the study had a role in study design, but had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 1, 2008, and Oct 31, 2012, we screened 1765 patients with type 2 diabetes and randomly assigned 264 (300/6) of 885 eligible patients to either IPT (n=133) or CPT (n=131; figure 1). Enrolled participants were predominantly men aged between 30 and 60 years (table 1). Baseline cardiometabolic risk profiles were similar between groups (table 1). There were no major

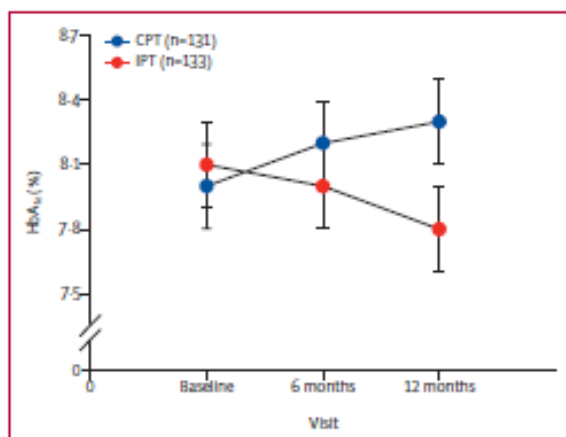


Figure 2: HbA_{1c} at baseline and follow-up visits at 6 and 12 months. Data are adjusted means and 95% CIs. p=0.5202 for between-group difference at 6 months; p=0.0345 for between-group difference at 12 months (no adjustment for baseline values, but adjusted for age, sex, ethnicity, smoking, duration of diabetes, and BMI). CPT-control periodontal treatment; IPT-intensive periodontal treatment.

anthropometric differences between groups, and participants did not report significant changes in their lifestyles or diets (assessed as overall caloric intake) during the study. 20 (8%) of 264 randomly assigned patients were lost to follow-up, with similar proportions in the two groups at 12 months (12 [9%] of 133 in the IPT group and eight [6%] of 131 in the CPT group; p=0.5434). Differences in some diabetes medications were seen at baseline between study groups (appendix).

After the 2 month review visit (which was booked 2 months from the initial whole mouth scaling session), 63 patients with good oral hygiene (dental plaque scores of $\leq 20\%$) and at least one 6 mm or deeper residual periodontal pocket had periodontal surgical therapy to improve access for root surface cleaning. 55 patients who still had suboptimum oral hygiene and 15 patients who did not have residual 6 mm or deeper periodontal pockets at 2 months received additional scaling of the root surfaces under local analgesia (n=70 in total).

HbA_{1c} was reduced in patients in the IPT group after 12 months of treatment compared with patients in the CPT group (figure 2). The difference in HbA_{1c} between patients in the IPT and CPT groups (adjusted for age, sex, ethnicity, smoking status, duration of diabetes, BMI, and baseline HbA_{1c}) was 0.3% (95% CI 0.0 to 0.5; p=0.074) at 6 months and 0.6% (0.3 to 0.9; p<0.0001) at 12 months (table 2). Per-protocol analysis showed a non-significant difference between groups at 6 months (0.1%, -0.3 to 0.5; p=0.6609) and a significant difference at 12 months (0.6%, 0.1 to 1.0; p=0.0101). Post-hoc analyses showed that 86 (65%) of 133 patients in the IPT group reached a 0.4% reduction in HbA_{1c} at 12 months versus 47 (36%) of 131 patients in the CPT group (p=0.0027); 89 (67%) of 133 patients in the IPT group versus 43 (33%) of 131 patients in the CPT group achieved a 0.9% reduction of HbA_{1c} at 12 months (p=0.0284). A post-hoc sensitivity analysis in subgroups of patients based on use of medications other than glucose-lowering drugs confirmed a consistent reduction in HbA_{1c} in the IPT group compared with the CPT group (appendix).

At 12 months, all clinical periodontal parameters were significantly better in patients in the IPT group than in patients in the CPT group (figure 3). Full mouth dental plaque scores were 18% (95% CI 13-23; p<0.0001) lower at 2 months, 20% (14-25; p<0.0001) lower at 6 months, and 21% (15-26; p<0.0001) lower at 12 months in the IPT group than in the CPT group. Full mouth bleeding scores were 16% (11-21; p<0.0001) lower at 2 months, 24% (19-29; p<0.0001) lower at 6 months, and 26% (21-31; p<0.0001) lower at 12 months in the IPT group than in the CPT group. Probing pocket depths were 0.6 mm (95% CI 0.4-0.7; p<0.0001) lower at 2 months and 0.8 mm (0.6-1.0; p<0.0001) lower at both 6 and 12 months after therapy in patients in the IPT group than in the CPT group (appendix). The IPT group had 23 (95% CI 17-28; p<0.0001) fewer periodontal pockets with a probing pocket depth greater

| | 2 months | | | | 6 months | | | | 12 months | | | |
|--|---------------|---------------|-----------------------|--------|-----------------|-----------------|----------------------------|---------|-----------------|-----------------|------------------------|---------|
| | CPT | IPT | Δ12M (95% CI) | pvalue | CPT | IPT | Δ6M (95% CI) | pvalue | CPT | IPT | Δ12M (95% CI) | pvalue |
| HbA _{1c} (%) | | | | | 8.1% (0.2) | 8.0% (0.2) | 0.3 (0.0to 0.5) | 0.074 | 8.3% (0.2) | 7.8% (0.2) | 0.6 (0.3 to 0.9) | <0.0001 |
| Total cholesterol (mmol/L) | 4.1 (0.1) | 4.3 (0.1) | 0.1 (-0.2 to 0.2) | 0.86 | 4.2 (0.1) | 4.3 (0.1) | 0.1 (-0.1 to 0.4) | 0.33 | 4.1 (0.1) | 4.2 (0.1) | 0.0 (-0.3 to 0.3) | 0.99 |
| HDL cholesterol (mmol/L) | 1.2 (0.0) | 1.3 (0.0) | 0.0 (0.0 to 0.1) | 0.57 | 1.2 (0.0) | 1.3 (0.0) | 0.0 (-0.1 to 0.1) | 0.58 | 1.3 (0.0) | 1.3 (0.0) | 0.1 (0.0 to 0.1) | 0.11 |
| LDL cholesterol (mmol/L) | 2.2 (0.1) | 2.3 (0.1) | 0.0 (-0.2 to 0.2) | 0.71 | 2.3 (0.1) | 2.3 (0.1) | 0.1 (-0.1 to 0.3) | 0.25 | 2.2 (0.1) | 2.2 (0.1) | 0.0 (-0.2 to 0.2) | 0.90 |
| Triglycerides (mmol/L) | 1.5 (0.1) | 1.6 (0.1) | 0.0 (-0.2 to 0.3) | 0.92 | 1.5 (0.1) | 1.1 (0.1) | 0.0 (-0.2 to 0.3) | 0.77 | 1.4 (0.1) | 1.6 (0.1) | -0.1 (-0.4 to 0.1) | 0.32 |
| Systolic blood pressure (mmHg) | 132 (1.4) | 131 (1.4) | 1.5 (-3.4 to 6.4) | 0.54 | 133 (1.4) | 131 (1.4) | 3.0 (-1.8 to 7.8) | 0.22 | 133 (1.4) | 130 (1.4) | 2.3 (-2.6 to 7.2) | 0.35 |
| Diastolic blood pressure (mm Hg) | 80 (0.9) | 80 (0.9) | 1.0 (-2.1 to 4.2) | 0.52 | 80 (0.8) | 81 (0.8) | -0.8 (-3.4 to 1.9) | 0.57 | 81 (0.9) | 79 (0.9) | 1.2 (-1.1 to 4.1) | 0.43 |
| BMI (kg/m ²) | 30.4 (0.5) | 30.1 (0.5) | 0.0 (-0.2 to 0.2) | 0.83 | 30.5 (0.5) | 30.1 (0.5) | 0.1 (-0.2 to 0.3) | 0.62 | 30.2 (0.5) | 30.0 (0.5) | 0.0 (-0.4 to 0.4) | 0.86 |
| Waist circumference (cm) | 104 (1.3) | 103 (1.3) | 0.6 (-2.8 to 4.1) | 0.72 | 103 (2.5) | 106 (2.5) | -3.2 (-10.2 to 3.8) | 0.37 | 105 (1.3) | 104 (1.3) | 1.2 (-2.3 to 4.6) | 0.51 |
| Fasting insulin (mIU/L) | 20.3 (4.6) | 14.6 (4.6) | 4.7 (-1.4 to 10.8) | 0.13 | 20.4 (4.4) | 19.0 (4.4) | -0.7 (-6.3 to 4.9) | 0.80 | 18.0 (3.1) | 17.2 (3.1) | -1.1 (-4.2 to 2.0) | 0.50 |
| Flow-mediated dilatation (%) | | | | | 3.8% (0.3) | 5.0% (0.3) | -0.9 (-1.2 to -0.5) | <0.0001 | 3.4% (0.2) | 4.8% (0.2) | -1.2 (-1.5 to -0.9) | <0.0001 |
| Fasting glucose (mg/dL) | | | | | 160.1 (5.2) | 148.1 (5.1) | 12.1 (2.3 to 22.1) | 0.0323 | 164.1 (5.2) | 151.1 (5.1) | 12.9 (3.4 to 21.0) | 0.0344 |
| Creatinine (μmol/L) | | | | | 83.1 (2.0) | 80.2 (2.1) | 1.8 (-2.9 to 6.5) | 0.231 | 83.1 (2.1) | 79.8 (2.1) | 4.8 (0.1 to 9.5) | 0.0421 |
| eGFR (ml/min per 1.73 m ²) | | | | | | | | | 87.1 (2.4) | 90.6 (2.6) | -4.1 (-6.8 to -1.4) | 0.0031 |
| HOMA2-cell function | | | | | 19.6 (2.3) | 19.6 (2.3) | -1.6 (-4.6 to 1.5) | 0.31 | 17.9 (1.8) | 18.7 (1.8) | 1.8 (-5.1 to 1.5) | 0.29 |
| HOMA2 insulin sensitivity | | | | | 444.7 (53.3) | 545.6 (53.5) | -122.1 (-265.8 to 21.5) | 0.10 | 461.8 (41.4) | 467.9 (41.6) | 0.5 (-89.2 to 90.6) | 0.99 |
| HOMA2 insulin resistance | | | | | 0.4 (0.1) | 0.5 (0.1) | 0.0 (-0.2 to 0.1) | 0.57 | 0.4 (0.0) | 0.4 (0.0) | 0.0 (0.0 to 0.1) | 0.14 |
| UKPDS10-year cardiovascular disease risk | | | | | | | | | 11.0% (1.1) | 8.8% (1.1) | 1.1 (1.0 to 1.2) | 0.0323 |

Data are unadjusted mean (SE), unless otherwise stated. p values are for the calculated Δ values, including adjustment for baseline values and other confounders. CPT=control periodontal treatment IPT=intensive periodontal treatment Δ12M=difference at 12 months between CPT and IPT groups, adjusted for baseline values and other confounders. Δ6M=difference at 6 months between CPT and IPT groups, adjusted for baseline values and other confounders. Δ12M=difference at 12 months between CPT and IPT groups, adjusted for baseline values and other confounders. eGFR=estimated glomerular filtration rate. HOMA2=homeostasis model assessment 2 UKPDS=UK Prospective Diabetes Study.

Table 2: Metabolic, vascular, and renal measures at baseline and at 2, 6, and 12 months' follow-up, by study group

than 4 mm than the CPT group at 2 months, 28 (23-34; $p < 0.0001$) fewer at 6 months, and 27 (22-32; $p < 0.0001$) fewer at 12 months. Post-hoc missing data analyses confirmed these results (data not shown). The main reason for extraction of unsalvageable teeth related to the study hypothesis was severe infection and inflammation, which would affect the study results; similar average numbers of teeth were removed from each study group (the mean number of teeth removed was 1.0 [95% CI 0.4--1.2]).

We saw a significant reduction in plasma fasting glucose concentrations after 6 months and 12 months of therapy in the IPT group compared with the CPT group (table 2). During the study, fasting insulin concen-

trations, HOMA2 scores, and lipids concentrations did not change between groups (table 2). We found no differences in HbA_{1c} between patients in the IPT subgroups (non-surgical [n=70] vs non-surgical and surgical therapy [n=63]) in a post-hoc analysis (appendix). Post-hoc missing data analyses confirmed these results (data not shown).

CRP concentrations were significantly lower in the IPT group than in the CPT group at 2 months, 6 months, and 12 months after treatment (table 3). *TNFα* concentrations were significantly lower in the IPT group than in the CPT group at 6 months and 12 months (table 3; appendix). We did not see significant differences in any other inflammatory or endothelial surface markers,

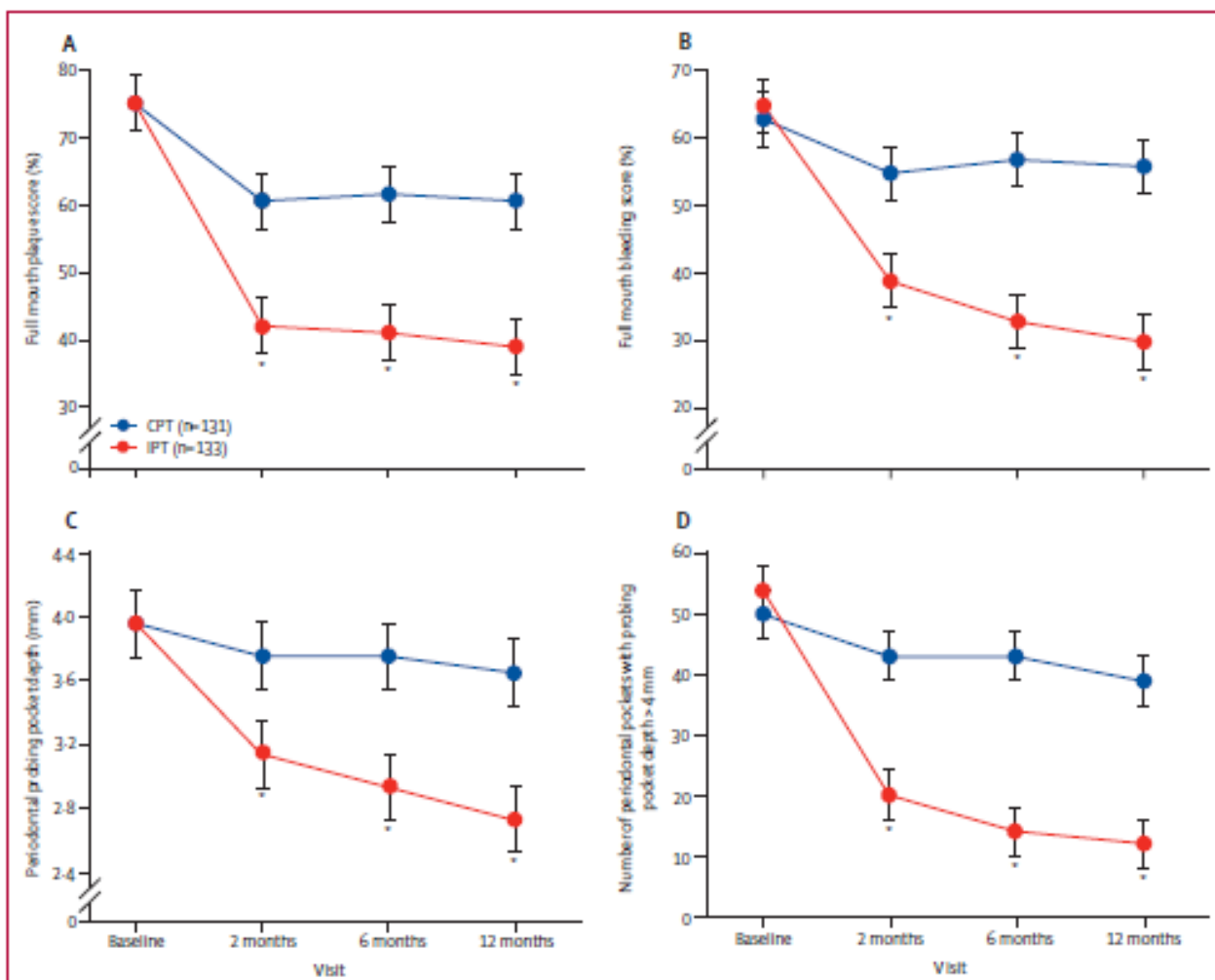


Figure 3: Periodontal measures at baseline and follow-up visits at 2, 6, and 12 months

Data are adjusted means and 95% CIs. CPT=control periodontal treatment IPT=intensive periodontal treatment. *Between-group differences for all periodontal measures were significant at 2, 6, and 12 months (all $p < 0.0001$).

apart from a difference in soluble E-selectin and P-selectin at 6 months (table 3). We saw no differences in CRP or TNF α concentrations between the IPT subgroups in the post-hoc analysis by corrective treatment subgroup (non-surgical vs non-surgical and surgical; appendix). Post-hoc missing data analyses confirmed these results (data not shown).

Patients in the IPT group had greater FMD at 6 months and 12 months than patients in the CPT group (table 2). We saw no major differences between groups in blood pressure measures (table 2). Patients in the IPT group had a lower overall coronary artery disease 10 year risk score than patients in the CPT group at 12 months (table 2). Post-hoc missing data analyses confirmed these results (data not shown).

At 12 months, creatinine levels were significantly lower in patients who received IPT than in patients receiving CPT (table 2). At 12 months, patients in the IPT group had higher eGFR than did patients in the CPT group (table 2). Post-hoc missing data analyses confirmed these results (data not shown).

Adverse events were similar between study groups (table 4). Four serious adverse events resulted in death (one in the IPT group and three in the CPT group; $p = 0.3683$; table 4). Changes in prescribed medications (>20% of patients) were similar between the two study groups (appendix). No significant differences in amount and type of diabetes medications post randomisation were seen between study groups. Post-hoc missing data analyses confirmed these results (data not shown).

Between-group differences in HbA $_{1c}$ at 12 months correlated with those in periodontal parameters (periodontal probing depth, RO 2 ; Spearman-rank correlation test, $p = 0.0074$; ρ coefficient 0.28, 95% CI 0.08 to 0.48), kidney function (eGFR, $R = -0.2$; Spearman-rank correlation test, $p = 0.0192$; ρ coefficient -0.19, 95% CI -0.28 to -0.03), and inflammatory outcomes (CRP, RO 2 ; Spearman-rank correlation test, $p = 0.0014$; ρ coefficient 0.05, 95% CI 0.01 to 0.08; and TNF α , $R = 0.2$; Spearman-rank correlation test, $p = 0.0013$; ρ coefficient 0.06, 95% CI 0.01 to 0.14). Similarly, between-group differences in CRP at 12 months

| | 2 months | | | | 6 months | | | | 12 months | | | |
|------------------------|----------------|----------------|-------------------------|--------|----------------|----------------|-----------------------|--------|----------------|----------------|-----------------------|--------|
| | CPT | IPT | Δ12M (95%CI) | pvalue | CPT | IPT | Δ16M (95% CI) | pvalue | CPT | IPT | Δ112M (95%CI) | pvalue |
| CRP(mg/L) | 3.7 (0.2) | 2.7 (0.2) | 1.2 (1.0 to 1.4) | 0.0213 | 4.0 (0.2) | 2.8 (0.2) | 1.3 (0.9 to 1.7) | 0.0102 | 3.3 (0.3) | 2.4 (0.2) | 1.0 (0.8 to 1.2) | 0.0102 |
| TNFα (pg/ml) | 4.3 (0.3) | 4.4 (0.2) | 0.2 (-0.4 to 0.8) | 0.67 | 4.6 (0.2) | 4.3 (0.2) | 0.6 (0.0 to 1.2) | 0.0434 | 4.6 (0.3) | 4.1 (0.3) | 0.4 (0.2 to 0.6) | 0.0201 |
| Interferon γ (pg/ml) | 2.9 (0.5) | 3.4 (0.5) | -1.6 (-3.1 to 0.2) | 0.14 | 6.6 (2.1) | 2.9 (2.3) | 0.8 (-7.0 to 8.6) | 0.84 | 2.5 (0.4) | 2.6 (0.5) | -0.7 (-2.2 to 0.8) | 0.37 |
| Interleukin 10 (pg/ml) | 6.9 (0.4) | T3 (0.4) | -0.3 (-1.5 to 0.8) | 0.57 | T3 (0.4) | T3 (0.4) | 0.1 (-0.8 to 1.0) | 0.86 | 7.6 (0.6) | 8.6 (0.6) | -0.1 (-1.9 to 1.6) | 0.87 |
| Interleukin 12 (pg/ml) | 3.2 (1.7) | 2.8 (1.8) | 0.3 (-2.0 to 2.6) | 0.79 | 3.9 (1.9) | 2.5 (2.1) | 0.8 (-2.6 to 4.1) | 0.65 | 3.1 (1.7) | 2.7 (1.8) | 0.9 (-0.8 to 2.7) | 0.28 |
| Interleukin 6 (pg/ml) | 2.0 (0.5) | 2.6 (0.5) | -0.9 (-2.3 to 0.5) | 0.21 | 2.3 (0.2) | 2.3 (0.2) | -0.2 (-0.8 to 0.5) | 0.61 | 2.2 (0.5) | 3.1 (0.5) | -1.1 (-2.3 to 0.0) | 0.06 |
| Interleukin 8 (pg/ml) | 17.2 (2.0) | 16.4 (2.0) | 0.4 (-5.1 to 5.9) | 0.89 | 18.3 (1.8) | 16.1 (1.8) | 1.1 (-3.1 to 5.8) | 0.66 | 17.6 (1.2) | 14.9 (1.2) | 2.5 (-0.9 to 6.0) | 0.15 |
| E-selectin (pg/ml) | 41.0 (3.0) | 35.6 (2.9) | -0.4 (-4.2 to 3.3) | 0.82 | 41.9 (2.7) | 33.0 (2.7) | 3.5 (0.4 to 6.7) | 0.0295 | 43.0 (2.9) | 36.8 (2.9) | 1.0 (-2.4 to 4.4) | 0.58 |
| P-selectin (pg/ml) | 139.0 (6.8) | 133.0 (6.8) | -0.1 (-13.4 to 13.2) | 0.99 | 140.4 (6.2) | 119.1 (6.2) | 15.0 (3.2 to 26.7) | 0.0127 | 150.1 (7.3) | 141.2 (7.2) | 42 (-8 to 17.2) | 0.52 |
| siCAM3 (pg/ml) | 5.8 (0.7) | 5.2 (0.7) | -0.1 (-0.7 to 0.5) | 0.79 | 5.9 (0.6) | 4.8 (0.6) | 0.5 (0.0 to 0.9) | 0.06 | 6.4 (0.7) | 5.3 (0.7) | 0.4 (-0.3 to 1.1) | 0.24 |
| Thrombomodulin (pg/ml) | 13.4 (1.3) | 12.0 (1.3) | -0.4 (-1.6 to 0.7) | 0.44 | 13.2 (1.2) | 10.7 (1.2) | 0.7 (-0.3 to 1.7) | 0.16 | 13.6 (1.2) | 11.6 (1.2) | 0.3 (-0.6 to 1.2) | 0.52 |

Data are unadjusted mean (SE), unless otherwise stated. p values are for the calculated *t* values, including adjustment for baseline values and other confounders. CPT=control periodontal treatment IPT=intensive periodontal treatment Δ12M=difference at 2 months between CPT and IPT groups, adjusted for baseline values and other confounders. Δ16M=difference at 6 months between CPT and IPT groups, adjusted for baseline values and other confounders. Δ112M=difference at 12 months between CPT and IPT groups, adjusted for baseline values and other confounders. CRP=C-reactive protein. TNFα=tumour necrosis factor α. siCAM3=soluble intercellular adhesion molecule-3.

Table 3: Inflammatory and endothelial surface markers

correlated with those in periodontal parameters (periodontal probing depth, $R=0.2$; Spearman-rank correlation test, $p=0.0062$; ρ coefficient 0.84, 95% CI 0.07 to 1.62) and *TNFα* ($R=0.3$; Spearman-rank correlation test, $p<0.0001$; ρ coefficient 0.22, 95% CI 0.10 to 0.54), and those of *TNFα* correlated with periodontal parameters (periodontal probing depth, $R=0.2$; Spearman-rank correlation test, $p=0.0214$; ρ coefficient 0.33, 95% CI 0.03 to 0.63). Lastly, changes in vascular function (FMD) correlated with improvement in periodontal parameters (periodontal probing depth, $R=0.2$; Spearman-rank correlation test, $p=0.0033$; ρ coefficient -0.32 , 95% CI -0.56 to -0.08 ; and gum bleeding scores, $R=0.2$; Spearman-rank correlation test, $p=0.0142$; ρ coefficient -0.01 , 95% CI -0.02 to -0.00). Post-hoc missing data analyses confirmed these results (data not shown).

Overall Audit of Diabetes Dependent Quality of Life scores showed better quality of life at 12 months in patients in the IPT group than in patients in the CPT group (0.83, 95% CI 0.29-1.38; $p=0.0034$). This was mainly due to changes in working life (difference 1.12, 95% CI 0.37-1.86; $p=0.0029$), self-confidence (difference 0.48, 0.17-1.22; $p=0.0413$), and living conditions (difference 0.81, 0.40-1.43; $p=0.0096$) domains of the test. Post-hoc missing data analyses confirmed these results (data not shown).

Discussion

Results of this study show that IPT improves metabolic control in patients with type 2 diabetes after 12 months compared with usual care. Reductions in HbA_{1c} and fasting plasma glucose concentrations were accompanied by improved vascular and kidney function, reduced systemic inflammation, and improved quality of life. These results suggest a causal relation between periodontitis and diabetes control and key complications of diabetes.

Our results suggest that oral health improvement in this population represents a novel and important therapeutic opportunity. Evidence from other studies¹⁸ suggests that every percent age point reduction in HbA_{1c} is associated with a 21% reduction in clinically relevant endpoints, including mortality. Metformin represents the first-line drug in the management of type 2 diabetes, but most patients struggle to achieve meaningful improvement in metabolic biomarkers with this drug alone. In this study, periodontal treatment was used as an adjunctive therapy to traditional glucose-lowering drugs. Evidence suggests that adding a second glucose-lowering drug results in an additional reduction in HbA_{1c}, ranging between 0.4 and 0.9 percentage points.¹⁹ The effect of intensive periodontal therapy on metabolic control as seen in this study is therefore similar in magnitude to that achieved by adding a second diabetes drug.

Many small trials and several meta-analyses have investigated the potential benefit of periodontitis treatment on glucose control, with inconclusive findings. Because most previous trials had a small sample size (<30 patients per group) and short follow-up, comparison with our study is difficult. A previous trial¹⁰ of periodontal

treatment and metabolic control by Sun and colleagues reported a significant reduction in HbA_{1c} of 0.4 percentage points after 3 months. In the trial, 157 patients with type 2 diabetes and periodontitis in at least 30% their gingival sites were randomly assigned to periodontal treatment, including non-surgical and surgical periodontal therapy and a systemic course of antibiotics, whereas the 75 participants in the control group received no treatment. In our study, we did not measure metabolic markers until 6 months after baseline, and the IPT and CPT groups in our trial were both substantially different to the treatment and control groups, respectively, used in the trial by Sun and colleagues. Despite these differences and the high risk of bias in the study by Sun and colleagues,¹⁰ the results of the study are consistent with our findings.

Two other trials^{21,22} reported null effects of periodontal therapy on metabolic control. In the post-hoc analysis of one trial,²¹ in which 165 male participants in the US Veterans Administration programme received periodontal treatment or usual care for 4 and 12 months in a two-by-two design, HbA_{1c} was numerically lower in the treatment group, but the results were not significant, possibly due to the small sample size. Another 6 month trial²² of 134 patients with periodontitis and type 2 diabetes involved a course of non-surgical periodontal therapy, but patients randomly assigned to the test group had an additional course of treatment after 3 months. In this trial, both treatment groups saw a reduction in HbA_{1c}, with no significant difference between groups. The smaller sample size, the different periodontal treatments provided, and the allocation bias are the main differences between our study and this other trial.

A 2015 Cochrane review²³ concluded that the level of evidence for the effect of periodontal treatment in patients with type 2 diabetes is of low quality, and that any improvement in glucose control after periodontal treatment is lost after 3–4 months. The largest trial to date (the multicentre Diabetes and Periodontal Therapy Trial [DPTT]), which had two study groups with 257 patients each²⁴ showed non-significant slight improvements in periodontal health and no benefit on glycaemic control at 6 months. Several factors might account for the difference between our findings and those of the DPTT. Our study was longer (12 months vs 6 months). As in the DPTT, our primary endpoint did not reach significance at 6 months, but we did see significant differences between groups at 12 months. Additionally, participants achieved greater reductions in dental plaque and gingival bleeding scores than those reported in the DPTT, emphasising the potential importance of controlling periodontal inflammation using effective periodontal therapy, which would include both non-surgical and surgical management of gum inflammation in the patient population. The use of a standardised periodontal treatment protocol in a single specialist centre might have strengthened our findings; however, whether these

| | Intensive periodontal therapy (n=133) | Control periodontal therapy (n=131) | p value |
|---|---------------------------------------|-------------------------------------|---------|
| Number of serious adverse events (any)* | | | 0.8244† |
| 21 | 11 (8%) | 11 (8%) | |
| 22 | 2 (2%) | 1 (1%) | |
| 23 | 1 (1%) | 1 (1%) | |
| Serious adverse events causing death | 1 (1%) | 3 (2%) | 0.3683 |
| Number of adverse events (any) | | | 0.3994‡ |
| 21 | 30 (23%) | 23 (18%) | |
| 22 | 33 (25%) | 38 (29%) | |
| 23 | 17 (13%) | 18 (14%) | |
| 24 | 12 (9%) | 17 (13%) | |
| 25 | 12 (9%) | 6 (5%) | |
| 26 | 7 (5%) | 3 (2%) | |
| 27 | 1 (1%) | 3 (2%) | |
| 28 | 3 (2%) | 1 (1%) | |
| Tooth pain† | 43 (4.0%) | 31 (3.0%) | 0.8910 |
| Tooth sensitivity† | 33 (3.1%) | 9 (0.9%) | 0.7327 |
| Tooth infection† | 27 (2.5%) | 27 (2.6%) | 0.6997 |
| Vaccination† | 21 (2.0%) | 24 (2.3%) | 0.1376 |
| Chest infection† | 13 (1.2%) | 11 (1.0%) | 0.5000 |
| Gum swelling† | 12 (1.1%) | 8 (0.8%) | 0.1521 |
| Tooth fracture† | 12 (1.1%) | 17 (1.6%) | 0.2271 |
| Tooth restoration† | 9 (0.8%) | 12 (1.1%) | 0.1332 |
| Headache† | 8 (0.8%) | 4 (0.4%) | 0.5578 |
| Influenza† | 7 (0.7%) | 7 (0.7%) | 0.3618 |
| Throat infection† | 4 (0.4%) | 5 (0.5%) | 0.4145 |
| Foot infection† | 5 (0.5%) | 6 (0.6%) | 0.5488 |
| Fainting† | 3 (0.3%) | 3 (0.3%) | 0.2733 |
| Dizziness† | 4 (0.4%) | 4 (0.4%) | 0.5134 |
| Back pain† | 3 (0.3%) | 5 (0.5%) | 0.3882 |

Data are n (%). *Serious adverse events reported in the intensive periodontal therapy group include toe gangrene, pneumonia, spine surgery, fall, ear accident, stroke, gastric surgery, coronary angioplasty, hypoglycaemia, confusion or disorientation, lung resection, kidney stones, and prostate hypertrophy; serious adverse events reported in the control periodontal therapy group include chest pain (heartburn), hypertensive crisis, femoral fracture, pneumonia, alcoholic liver disease, acute episode of irritable bowel syndrome, spine surgery, and hip replacement. †The p value is an overall comparison of the numbers of all serious adverse events between groups. ‡The serious adverse event resulting in death reported in the intensive periodontal therapy group was acute kidney failure; serious adverse events resulting in death reported in the control periodontal therapy group were myocardial infarction, heart failure, and stroke. §The p value is an overall comparison of the numbers of all adverse events (including serious adverse events) between groups. ¶Denominators for calculation of percentages are total number of events (n=1064 in the intensive periodontal therapy group; n=1048 in the control periodontal therapy group).

Table 4: Adverse events

findings could be replicated in multicentre, larger trials is unclear. Finally, our study participants differed from those in the DPTT: our participants were aged 18 years or older with at least 20 periodontal sites with active periodontal inflammation, whereas in the DPTT, the patients were aged 35 years or older with a minimum of two sites with periodontal inflammation. As a result, a smaller proportion of patients in the DPTT had gum inflammation to start with than in our study. At the end of the DPTT, many of the test patients still had ongoing gum inflammation and could have been re-enrolled into the same study.

In our study, we found improvements in a broad range of secondary outcomes, suggesting an effect of periodontal therapy on cardiovascular and renal complications of diabetes. In a previous randomised clinical trial⁷ in patients without diabetes, we showed that IPT led to significantly improved endothelial function after 6 months of treatment. We now show that this improvement can be maintained up to 1 year in a population with diabetes who are at high risk for cardiovascular disease. Additionally, we report a 1-1% lower overall UKPDS 10 year risk of cardiovascular disease with IPT than with CPT at 12 months. This estimate must be interpreted cautiously rather than as definitive evidence to be applied in clinical practice. Findings from the UKPDS for metformin or insulin versus conventional glucose lowering with diet restriction showed only a marginal improvement in cardiovascular mortality despite a 0-9% reduction in HbA_{1c}.¹ Periodontal treatment might improve overall cardiovascular risk beyond the glucose lowering effect; if demonstrated in larger intervention trials, periodontitis might represent a novel preventable cause of vascular complications in patients with diabetes.

The change in HbA_{1c} was accompanied by improved eGFR in our study, suggesting a causal relation between periodontitis and increased renal and cardiovascular complications, as has been postulated from at least one observational study.²⁵ Glomerular endothelial damage is regarded as an early step in the evolution of diabetic nephropathy.²⁶ A reduction in the thickness of the endothelial glycocalyx has been described in patients with early stages of diabetic nephropathy²⁷ and the observed beneficial effect of IPT on endothelial function might link the improvements in FMD and renal function that we observed.

The IPT group reported better diabetes-related quality of life than the CPT group in our study. A systematic review²⁸ found that no relevant studies reported data on quality of life; a gap partly addressed by our study. Our results showed that the overall improvements were mainly due to increased psychological and functional aspects of quality of life, with differences reported in both self-confidence and living conditions. Furthermore, IPT resulted in improvement of the working life of patients with diabetes, highlighting the potentially wide societal impact of such treatment.

Inflammation is a known driver of insulin resistance, with a role in the initiation and evolution of cardiovascular and renal complications in patients with and without diabetes.²⁸ Our findings support the hypothesis that reduction of periodontal inflammation is associated with reduced systemic inflammation and improved vascular function and metabolic markers, as suggested in a 2015 systematic review.⁵ TNF α has been implicated in systemic insulin sensitivity,²⁹ and the severity of periodontitis correlates linearly with systemic levels of TNF α in patients with diabetes.³⁰ We saw a linear correlation between reductions from baseline to 12 months in markers of systemic inflammation (CRP and TNF α), periodontal inflammatory parameters (probing pocket depths, number of deeper periodontal pockets, and gingival bleeding), and systemic outcomes (metabolic control and vascular and kidney functions). However, these correlations were not seen for measures of insulin production and sensitivity (HOMA2 scores). Previous reports have shown that reduction of inflammation by lifestyle interventions³¹ or drug therapy (eg, interleukin-1 antagonists)³² increases secretion of insulin from β cells and decreases blood glucose concentrations in patients with diabetes. In a large secondary prevention trial³³ of patients at high risk of cardiovascular diseases and other comorbidities including type 2 diabetes, treatment with an interleukin-1 β inhibitor (canakinumab) significantly lowered the rate of recurrent cardiovascular events versus placebo; this result was independent from the reductions in lipids achieved with drugs. Whether treatment of periodontitis, and the associated reduction in systemic inflammation, could produce similar benefits on outcomes such as cardiovascular and renal events in patients with type 2 diabetes could be addressed in future studies.

Our study has some limitations. In particular, our findings could be partly attributed to the effect of non-diabetes medications. Patients in the CPT and IPT groups presented with some differences in their use of aspirin, β blockers, and angiotensin-II blockers at baseline. We cannot exclude that medications used might have contributed to the differences in HbA_{1c} between study groups at 12 months. However, a post-hoc sensitivity analysis in subgroups of patients not taking these medications lent support to a consistent reduction in HbA_{1c} in the IPT group compared with the CPT group. Future studies should address the efficacy of periodontal treatment in patients with type 2 diabetes during treatment with different cardiometabolic drugs. We did this study in a single university centre and patients with moderate-to-severe periodontitis were treated for 12 months. We acknowledge a potential recruitment bias in this study and urge caution in extrapolating the results to all patients with type 2 diabetes; nevertheless, we aimed to reduce bias by recruiting from both hospital and primary-care recruitment centres (dental and medical).

Global prevalence of periodontal diseases is higher than 50%. In people with diabetes, the prevalence of severe

forms of periodontitis is almost 50%.³⁴ Our findings highlight the potential to improve metabolic control and possibly diabetes outcomes by addressing poor oral health in those with diabetes. Longer and larger studies are needed to determine whether the benefits we have shown are sustained beyond 12 months, are broadly applicable to people with type 2 diabetes, can reduce morbidity and mortality, and can improve quality of life in the long term. If confirmed in larger trials, diabetes care should incorporate routine oral health assessment and treatment as part of lifelong disease management.

Contributors

FD'A, SH, ADH, ND, and JED conceived of and designed the study. FD'A, NG, DB, MO, JS, GT, and members of the TASTE Group (appendix) collected data. Members of the TASTE Group and MO did the laboratory analyses. FD'A, SH, TK, SM, ADH, GT, ND, and JED interpreted the data. FD'A, SH, TK, SM, ADH, GT, ND, and JED drafted or critically revised the report. All authors approved the final submitted version of the report. FD'A, ND, and JED had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

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