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Effect of Periodontal Treatment on HbA1c among Patients with Prediabetes

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Abstract

Evidence is limited regarding whether periodontal treatment improves hemoglobin A1c (HbA1c) among people with prediabetes and periodontal disease, and it is unknown whether improvement of metabolic status persists >3 mo. In an exploratory post hoc analysis of the multicenter randomized controlled trial "Antibiotika und Parodontitis" (Antibiotics and Periodontitis)—a prospective, stratified, double-blind study—we assessed whether nonsurgical periodontal treatment with or without an adjunctive systemic antibiotic treatment affects HbA1c and high-sensitivity C-reactive protein (hsCRP) levels among periodontitis patients with normal HbA1c (≤5.7%, $n = 218$), prediabetes (5.7% < HbA1c < 6.5%, $n = 101$), or unknown diabetes (HbA1c ≥ 6.5%, $n = 8$) over a period of 27.5 mo. Nonsurgical periodontal treatment reduced mean pocket probing depth by >1 mm in both groups. In the normal HbA1c group, HbA1c values remained unchanged at 5.0% (95% CI, 4.9% to 6.1%) during the observation period. Among periodontitis patients with prediabetes, HbA1c decreased from 5.9% (95% CI, 5.9% to 6.0%) to 5.4% (95% CI, 5.3% to 5.5%) at 15.5 mo and increased to 5.6% (95% CI, 5.4% to 5.7%) after 27.5 mo. At 27.5 mo, 46% of periodontitis patients with prediabetes had normal HbA1c levels, whereas 47.9% remained unchanged and 6.3% progressed to diabetes. Median hsCRP values were reduced in the normal HbA1c and prediabetes groups from 1.2 and 1.4 mg/L to 0.7 and 0.7 mg/L, respectively. Nonsurgical periodontal treatment may improve blood glucose values among periodontitis patients with prediabetes (ClinicalTrials.gov NCT00707369).

Keywords: clinical trial, subgroup analysis, periodontitis, hemoglobin A1c, prediabetic state, C-reactive protein

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A supplemental appendix to this article is available online.

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Introduction

The prevalence of diabetes continues to rise worldwide. Between 2015 and 2040, the global prevalence of type 2 diabetes mellitus (T2DM) is predicted to increase from 8.8% to 10.4% (Ogurtsova et al. 2017). Between 9.3% and 55% of persons with prediabetes annually converted to T2DM within 3 y (Kerrison et al. 2017). Because the majority of people with prediabetes might progress to diabetes during the lifetime, the burden of T2DM could be reduced if prediabetes treatment covered a large part of the population at risk (Tabak et al. 2012). Prediabetes is related to increased mortality, morbidity, and health care costs, thus constituting an important public health problem. Alleviating the progression of prediabetes to T2DM is a reasonable way to reduce the diabetes epidemic and lessen health care costs. Indeed, lifestyle modifications or drug interventions among persons with prediabetes reduced the incidence of diabetes by 25% to 72% during 2-, 4-, and 6-y intervention periods (Eyre et al. 2004), and short-term glycemic control regressed to normoglycemia for many subjects with lifestyle modification. Although glycemic control worsened again over 3 to 5 y, it was still superior versus baseline results and control groups (Kerrison et al. 2017).

Elevated serum levels of C-reactive protein (CRP) were observed among prediabetic subjects over normoglycemic subjects, whereas no further CRP increase was observed between prediabetes and manifest diabetes, which may reflect early activation of the immune system (Grossmann et al. 2015). Higher serum levels of inflammatory markers were associated with the development of T2DM (Bo et al. 2017; Koloverou et al. 2017). Adjunctive treatment with anti-inflammatory drugs among subjects with prediabetes (Faghihimani et al. 2012) or T2DM (Larsen et al. 2007; Goldfine et al. 2013) reduced hemoglobin A1c (HbA1c) and inflammatory markers.

Periodontitis is a highly prevalent, bacterially induced inflammatory oral disease that results in pocket formation and breakdown of alveolar bone. Periodontitis is linked with a higher risk of HbA1c progression and diabetes through systemic low-grade inflammation (Demmer et al. 2008). Through an ulcerated periodontal pocket epithelium, oral pathogens or their metabolic products can enter the bloodstream during toothbrushing or chewing (Lockhart et al. 2008), in turn provoking an immune response and causing low-grade systemic inflammation. Another pathway may be leakage of proinflammatory cytokines into the main bloodstream, which might also affect the metabolic state (Loos et al. 2000).

Periodontal treatment reduces serum levels of inflammatory markers. A meta-analysis of clinical trials that investigated the effect of periodontal treatment on HbA1c levels found an HbA1c decrease of 0.29% at 3 mo after periodontal treatment (Simpson et al. 2015). All these studies, however, were performed on patients with long-standing diabetes, and periodontal treatment was only an adjunct to routine medical antidiabetic treatment. To date, studies evaluating the effects of periodontal scaling on metabolic control among persons with prediabetes reported inconsistent results (Faghihimani et al. 2013; Javed et al. 2014; Alshehri and Javed 2015).

The use of antibiotics as an adjunct to subgingival scaling reduced more periodontal pockets than did scaling alone (Harks et al. 2015). The consumption of amoxicillin significantly decreased positive blood culture results after toothbrushing (Lockhart et al. 2008), whereas more recent literature is equivocal regarding whether antibiotics as an adjunct to scaling has an additional impact on inflammatory markers (Demmer et al. 2013; Giannopoulou et al. 2016). Adjunctive intake of antibiotics did not improve hyperglycemia among uncontrolled patients with T2DM over scaling alone (Simpson et al. 2015). Furthermore, for people with prediabetes, 7-d amoxicillin intake did not affect insulin sensitivity or systemic low-grade inflammation (Reijnders et al. 2016).

In an exploratory subgroup analysis of the multicenter (8 university hospital centers) randomized controlled trial "Antibiotika und Parodontitis" (Antibiotics and Periodontitis; ABPARO), we examined whether nonsurgical periodontal treatment with or without an adjunctive systemic antibiotic treatment 1) affects HbA1c levels among periodontitis patients with normal HbA1c, prediabetes, or unknown diabetes and 2) decreases the proportion of periodontitis patients with prediabetes over a period of 27.5 mo.

Research and Design Methods

Study Design

This is an exploratory analysis of data from the prospective ABPARO trial with a parallel-group design (Current Controlled Trials ISRCTN64254080; ClinicalTrials.gov NCT00707369). The stratified double-blind ABPARO trial assessed the effect of an adjunctive antibiotic treatment in addition to scaling on the progression of periodontal disease (Harks et al. 2014). The protocol, details of the trial and procedures, and a description of the periodontal treatment are available in the Appendix.

Study Population

Out of 345 patients from the per-protocol collective of the main study, 17 were excluded because of known diabetes and 1 because of missing baseline HbA1c levels, leaving 327 patients. In the multivariable analysis, 1 further patient was excluded because of missing data (n = 326). Both treatment groups were pooled for the current analysis since, in terms of treatment allocation, there were no statistically significant differences either in HbA1c levels (interaction between treatment and visit: B = −0.054 [95% CI, −0.210 to 0.102] for 15.5 mo and B = −0.125 [95% CI, −0.291 to 0.041] for 27.5 mo; covariate-adjusted mixed model; per-protocol sample; Appendix Table 5) or in high-sensitivity CRP (hsCRP) levels (log-transformed; interaction between treatment and visit: B = −0.0001 [95% CI, −0.202 to 0.202] for 15.5 mo and B = 0.006 [95% CI, −0.200 to 0.212] for 27.5 mo; covariate-adjusted mixed model; per-protocol sample; Appendix Table 6). On the basis of their baseline HbA1c levels, patients were stratified into 218 subjects with normal HbA1c, 101 prediabetes subjects, and 8 subjects with previously unknown diabetes.

Table 1. Baseline Patient Characteristics According to Baseline HbA1c Status.

	Normal HbA1c[a] (*n* = 218)	Prediabetes[b] (*n* = 101)	Diabetes[c] (*n* = 8)
Age, y	51.7 ± 10.8	54.0 ± 9.2	59 ± 8.1
Sex			
Male	104 (48)	53 (52)	4 (50)
Female	114 (52)	48 (48)	4 (50)
Treatment			
Placebo	113 (52)	50 (50)	2 (25)
Antibiotics	105 (48)	51 (50)	6 (75)
Body mass index, kg/m^2	25.3 ± 4.4	26.1 ± 4.1	28.7 ± 6.2
<25	114 (52)	46 (45)	2 (25)
≥25 to <30	78 (36)	37 (37)	4 (50)
≥30	26 (12)	18 (18)	2 (25)
Current smoking status			
Nonsmoker	163 (75)	69 (68)	6 (75)
Smoker	55 (25)	32 (32)	2 (25)
Number of teeth	26 (23; 28)	25 (23; 27)	23.5 (22; 26)

Data are presented as mean ± SD, median (25% quantile; 75% quantile), or *n* (%).
HbA1c, hemoglobin A1c.
[a]HbA1c ≤5.7% or ≤38.8 mmol/mol.
[b]5.7% < HbA1c < 6.5% or 38.8 mmol/mol < HbA1c < 47.54 mmol/mol.
[c]HbA1c ≥ 6.5% or ≥47.54 mmol/mol.

Statistical Analyses

Statistical analyses were performed with SAS software (version 9.4; SAS Institute). *P* values and confidence intervals were intended to be exploratory, not confirmatory. Therefore, neither global nor local significance levels were determined, and no adjustment for multiplicity was applied. Exploratory *P* values ≤0.05 were considered statistically relevant.

Categorical variables were shown as frequencies (percentages). Normally distributed variables were presented as mean ± SD; nonnormally distributed variables were described by median (25% and 75% quantiles). The change of HbA1c group affiliation between baseline and follow-up visits (15.5 and 27.5 mo) was described with contingency tables and analyzed with marginal homogeneity tests (Stuart 1955). Spearman correlation coefficients (r_{Sp}) were calculated.

Multivariable analyses were performed to estimate covariate-adjusted effects of baseline HbA1c status and visit on HbA1c levels at follow-up visits. To account for missing values (treated as missing at random) and dependencies among repeated measurements, linear mixed models were fitted (Verbeke and Molenberghs 2000). Independent variables included HbA1c group (baseline), visit, and the interaction between HbA1c group (baseline) and visit, as well as baseline levels of treatment, age, sex, body mass index (BMI), and smoking status. Repeated measurements of HbA1c were modeled with heterogeneous residual covariance variance (unstructured) with the patient as the subject. Such a variance structure takes into account that within-group variance of baseline HbA1c levels is artificially restricted due to categorization. This means we allow the residual variance to be different for each visit, as well as the covariance between the different measurements. In our model, the estimated residual variances increased slightly from baseline to 15.5 mo and 27.5 mo. Results were reported as linear regression coefficients (B) and corresponding 95% CIs. Furthermore, least square means of HbA1c (percentage; with 95% CIs and *P* values) were estimated for linear combinations of coefficients adjusted for covariates.

Results

Study Participants

Periodontitis patients with prediabetes (54.0 ± 9.2 y) were 2.3 y older than those with normal HbA1c levels (51.7 ± 10.8 y) and 5 y younger than periodontitis patients with unknown diabetes (59.0 ± 8.1 y; Table 1). Furthermore, they were slightly more obese or overweight than their counterparts with normal HbA1c.

Crude Effects of Periodontal Treatment on HbA1c Levels and Conversion of HbA1c Status

In all 3 groups, periodontal treatment noticeably reduced mean levels of pocket probing depth (PPD; Table 2). Median hsCRP values decreased in the normal, prediabetes, and diabetes groups from 1.2, 1.4, and 1.6 to 0.7, 0.7, and 0.9 mg/L, respectively (group-specific changes in HbA1c levels described in detail later).

For periodontitis patients with normal HbA1c levels, mean HbA1c values remained unchanged at 5.0% (15.5-mo visit: 95% CI, 4.9% to 6.1%; 27.5-mo visit: 95% CI, 4.9% to 6.1%) during the observation period (Table 2, Figure A). However, 14.5% progressed to prediabetes and 1.4% to diabetes after 27.5 mo, while 84.1% remained at normal HbA1c levels (Table 3). This pattern was also obvious for the individual courses (Figure B).

Table 2. Periodontal and Laboratory Measurements at Baseline, 15.5-mo Examinations, 27.5-mo Examinations, and Respective Changes from Baseline.

Visit	Observed Value	Change from Baseline
	Normal HbA1c[a]	
Mean PPD, mm		
Baseline	3.4 ± 0.7	
15.5 mo	2.5 ± 0.6	–0.9 ± 0.6
27.5 mo	2.5 ± 0.6	–0.9 ± 0.7
Bleeding on probing, %		
Baseline	33.3 (21.8; 47.2)	
15.5 mo	12.5 (6.5; 22.2)	–19.4 (–31.5; –5.4)
27.5 mo	11.8 (6.3; 23.9)	–18.9 (–33.3; –5.9)
HbA1c, %		
Baseline	5.0 ± 0.6	
15.5 mo	5.0 ± 0.6	0.0 ± 0.7
27.5 mo	5.0 ± 0.7	0.0 ± 0.8
HbA1c, mmol/mol		
Baseline	31.1 ± 6.3	
15.5 mo	31.0 ± 6.8	–0.1 ± 7.9
27.5 mo	31.3 ± 7.9	0.1 ± 8.6
hsCRP, mg/L		
Baseline	1.2 (0.5; 2.8)	
15.5 mo	0.7 (0.4; 1.4)	–0.3 (–1.4; 0.0)
27.5 mo	0.7 (0.4; 1.3)	–0.5 (–1.5; 0.0)
	Prediabetes[b]	
Mean PPD, mm		
Baseline	3.7 ± 0.7	
15.5 mo	2.7 ± 0.7	–1.0 ± 0.7
27.5 mo	2.5 ± 0.7	–1.1 ± 0.8
Bleeding on probing, %		
Baseline	33.3 (25.0; 50.0)	
15.5 mo	12.5 (6.2; 21.7)	–19.0 (–31.0; –6.3)
27.5 mo	13.2 (5.0; 22.7)	–19.6 (–30.4; –9.0)
HbA1c, %		
Baseline	5.9 ± 0.2	
15.5 mo	5.4 ± 0.5	–0.5 ± 0.5
27.5 mo	5.6 ± 0.6	–0.4 ± 0.6
HbA1c, mmol/mol		
Baseline	41.2 ± 2.3	
15.5 mo	35.3 ± 5.7	–5.9 ± 5.5
27.5 mo	37.4 ± 6.9	–3.9 ± 6.6
hsCRP, mg/L		
Baseline	1.5 (0.8; 3.1)	
15.5 mo	0.8 (0.5; 1.5)	–0.4 (–1.7; 0.0)
27.5 mo	0.7 (0.4; 1.3)	–0.6 (–2.0; –0.2)
	Diabetes[c]	
Mean PPD, mm		
Baseline	3.8 ± 0.6	
15.5 mo	2.5 ± 0.3	–1.3 ± 0.7
27.5 mo	2.4 ± 0.2	–1.4 ± 0.7
Bleeding on probing, %		
Baseline	36.2 (22.9; 53.6)	
15.5 mo	11.2 (6.5; 14.9)	–22.1 (–44.9; –10.8)
27.5 mo	13.9 (3.6; 20.8)	–28.5 (–51.7; –2.7)
HbA1c, %		
Baseline	6.6 ± 0.1	
15.5 mo	5.7 ± 0.9	–0.9 ± 0.8
27.5 mo	5.7 ± 0.7	–0.9 ± 0.6
HbA1c, mmol/mol		
Baseline	49.0 ± 1.5	
15.5 mo	38.9 ± 9.7	–10.1 ± 9.2
27.5 mo	38.8 ± 7.6	–10.2 ± 7.0
hsCRP, mg/L		
Baseline	1.6 (1.1; 5.6)	
15.5 mo	1.2 (0.7; 1.5)	–0.5 (–4.1; –0.2)
27.5 mo	0.9 (0.5; 1.6)	–0.7 (–4.7; –0.2)

Data are presented as mean ± SD or median (25% quantile; 75% quantile).
HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; PPD, pocket probing depth.
[a]HbA1c ≤5.7% or ≤38.8 mmol/mol.
[b]5.7% < HbA1c < 6.5% or 38.8 mmol/mol < HbA1c < 47.54 mmol/mol.
[c]HbA1c ≥ 6.5% or ≥47.54 mmol/mol.

In the prediabetes group, mean HbA1c decreased from 5.9% (95% CI, 5.9% to 6.0%) to 5.4% (95% CI, 5.3% to 5.5%) after 15.5 mo and rebounded to 5.6% (95% CI, 5.4% to 5.7%) after 27.5 mo (Table 2, Figure A). Furthermore, change in mean PPD during the 27.5-mo follow-up period correlated weakly but positively with change in HbA1c levels among patients with prediabetes (r_{Sp} = 0.17, excluding subjects with hsCRP >10 mg/L at any visit), but an association cannot be concluded. In terms of visit-dependent conversions of the HbA1c status (Table 3), 30% remained in the prediabetes state after 15.5 mo, whereas 69% had normal HbA1c levels and only 1 patient progressed to diabetes. After 27.5 mo, the proportion of subjects with normal HbA1c levels decreased to 45.8%, while 47.9% had prediabetes and 6.3% had diabetes. Increasing variances of HbA1c levels within visits were also evident from individual trajectory plots (Figure B), confirming that a high proportion of periodontitis patients with prediabetes converted to the normal HbA1c group.

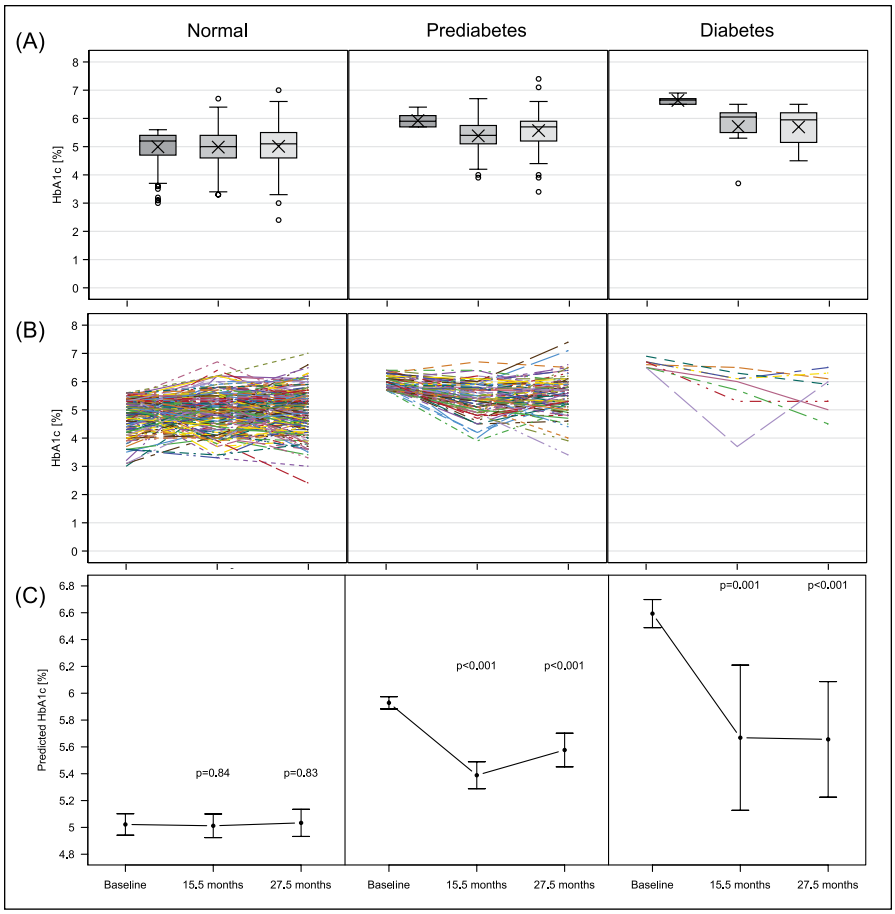

Figure. Graphical representation of observed values and model predicted margins of hemoglobin A1c (HbA1c). (**A**) Boxplot showing HbA1c levels over visits stratified by baseline HbA1c status. Values are presented as median, 25% and 75% quantiles, whiskers corresponding to minimum and maximum values within the interval [25% quantile - 1.5 × interquartile range, 75% quantile + 1.5 × interquartile range], and outliers (× denotes the mean). (**B**) Individual courses of HbA1c levels over visits stratified by baseline HbA1c status (each line denotes 1 patient). (**C**) Predicted margins (least square means with 95% CIs) of HbA1c from the linear mixed model grouped by baseline HbA1c status and visit. Covariate-adjusted *P* values are presented for comparisons with baseline Hba1c levels within groups defined by baseline HbA1c status. The underlying linear mixed model and estimated average HbA1c levels for pairwise group comparisons are presented in Appendix Tables 1 and 2.

In the unknown diabetes group, mean HbA1c dropped from 6.6% (95% CI, 6.5% to 6.8%) to 5.7% (95% CI, 5.0% to 6.5%) after 15.5 mo and persisted at 5.7% (95% CI, 5.1% to 6.3%) until the end of the observation period (Table 2, Figure A). Of 8 subjects with unknown diabetes at baseline, only 1 patient still had an HbA1c level in the diabetic range after 27.5 mo; the remaining 7 subjects changed to prediabetes (n = 4) or normal HbA1c (n = 3) after 27.5 mo (Table 3). Individual courses (Figure B) revealed that for patients converting to a better HbA1c status after 27.5 mo (n = 7), HbA1c levels were consistently reduced over 27.5 mo.

Adjusted Effects of Periodontal Treatment on HbA1c Levels

With the per-protocol sample, covariate-adjusted linear mixed models (Appendix Tables 1 and 2) revealed that HbA1c levels did not change statistically in the group with normal HbA1c but decreased noticeably between baseline and both follow-up visits in the prediabetic and diabetic groups (see Figure C for predicted margins of HbA1c). In the prediabetic and unknown diabetes groups, estimated mean HbA1c levels changed by −0.352% (95% CI, −0.472% to −0.231%; $P < 0.001$) and −0.938% (95% CI, −1.355% to −0.520%; $P < 0.001$), respectively, over 27.5 mo (Figure C, Appendix Table 2). Additionally, increasing body mass index was associated with increasing mean HbA1c levels ($P = 0.07$), whereas a noticeable influence of age, treatment, and smoking status on HbA1c could not be detected (all $P > 0.05$; Appendix Table 1).

With the intention-to-treat sample, results were consistent such that HbA1c levels decreased noticeably between baseline and both follow-up visits in the prediabetic and diabetic groups (Appendix Tables 3 and 4).

Table 3. Change of HbA1c Status between Baseline and 15.5- or 27.5-mo Examinations.

		HbA1c Status at 15.5 mo (n = 321)			
HbA1c Status at Baseline	Baseline, n	Normal	Prediabetes	Diabetes	P Value
Normal	213	189 (88.7)	23 (10.8)	1 (0.5)	
Prediabetes	100	69 (69.0)	30 (30.0)	1 (1.0)	
Diabetes	8	2 (25.0)	5 (62.5)	1 (12.5)	<0.001
		HbA1c Status at 27.5 mo (n = 318)			
Normal	214	180 (84.1)	31 (14.5)	3 (1.4)	
Prediabetes	96	44 (45.8)	46 (47.9)	6 (6.3)	
Diabetes	8	3 (37.5)	4 (50.0)	1 (12.5)	0.27

Results are reported as n (%; by row). P values are from marginal homogeneity tests (Stuart-Maxwell).
HbA1c, hemoglobin A1c.

Discussion

Among persons with prediabetes, nonsurgical periodontal treatment halved their number to 48% after 27.5 mo as compared with baseline, and mean HbA1c levels were reduced from 5.9% to 5.6% irrespective of adjunctive antibiotic therapy. In parallel to HbA1c improvements, reductions in local periodontal inflammation, pocket depths, and low-grade systemic inflammation were observed. In covariate-adjusted models, nonsurgical periodontal treatment reduced HbA1c by 0.352% over 27.5 mo. Among periodontitis patients with normal HbA1c, mean HbA1c levels did not change, but 14.5% of subjects progressed to prediabetes and 1.4% to diabetes, although low-grade systemic inflammation was reduced over the complete time span.

Study results for periodontitis patients with prediabetes are in agreement with previously published short-term trials (Javed et al. 2014; Lalla et al. 2015) reporting that HbA1c levels decreased significantly after periodontal treatment among people with prediabetes (Javed et al. 2014) and unknown diabetes (Lalla et al. 2015) after 3 and 6 mo, respectively. An HbA1c reduction of 0.3% to 0.5% is comparable to that achieved among periodontally treated patients with pharmacologically managed diabetes (Simpson et al. 2015). Taken together, these results support the idea that periodontitis patients who are unaware of their metabolic status might benefit from periodontal treatment.

A mean HbA1c decrease of 0.3% to 0.4% is comparable to reductions reached with lifestyle or drug interventions among people with prediabetes (Chiasson 2007). In the Diabetes Prevention Program Outcomes Study, the risk of developing T2DM was 56% lower among subjects who returned to normal glycemic control as compared with permanently prediabetic subjects (Perreault et al. 2012). In our study, the reduction of low-grade inflammation in the prediabetes group persisted over 27.5 mo, whereas HbA1c levels rebounded from 15.5 to 27.5 mo, as did the percentage of prediabetic subjects from 30% to 47.9%. It is probable that periodontal treatment improved insulin sensitivity via reduced systemic inflammation and thus delayed the progression from prediabetes to beta-cell dysfunction as it is observed in diabetes mellitus. Comparable results were observed in the Diabetes Prevention Program Outcomes Study, whose authors concluded that "prediabetes is a high-risk state for diabetes. . . . Reversion to normal glucose regulation, even if transient, is associated with a significantly reduced risk of future diabetes" (Perreault et al. 2012).

Overall, our results are consistent with findings from pharmacologic studies of prediabetes patients demonstrating that—irrespective of the drugs used—drug treatment only delayed diabetes onset rather than preventing it (Kanat et al. 2015). The authors argued that greater glycemic improvement was brought about by enhanced insulin sensitivity rather than improved beta-cell function.

In our study, hsCRP reduction over 27.5 mo ranged between −0.5 and −0.7 mg/L. A meta-analysis raised the question of whether a modest short-term CRP reduction of 0.4 mg/L after periodontal therapy would translate into any clinical benefit (Demmer et al. 2013). Regarding persons with prediabetes, our results suggest that even such a modest hsCRP reduction improves hyperglycemia to an extent comparable to that of daily adjunctive intake of anti-inflammatory drugs among diabetic subjects, besides established antidiabetic drugs (Goldfine et al. 2013) or metformin. Thus, one might deduce some clinical benefit for periodontal treatment among periodontitis patients with prediabetes.

The Centers for Disease Control and Prevention (2014) reported that 37% of US adults aged ≥20 y had prediabetes from 2009 to 2012, and 45.9% had moderate to severe periodontitis (Eke et al. 2015). In our patient population as well as others (Holm et al. 2016), about one-third of periodontally diseased subjects had prediabetes. Given that approximately 30% to 40% of the population has moderate or severe periodontitis (Konig et al. 2010), periodontal treatment may influence prediabetes in the general population. However, to affect HbA1c, periodontal treatment must be performed to high standards, and patients must be compliant with maintenance sessions to maintain healthy periodontal conditions.

In this study, 14.5% (n = 31) of periodontitis patients with normal baseline HbA1c levels progressed to prediabetes, and 1.4% subjects (n = 3) progressed to diabetes after 27.5 mo, although mean PPD and hsCRP levels were on average reduced over the complete time span. This finding shows that despite

effective periodontal treatment, glycemic control worsened for 1 in 8 patients with normal baseline HbA1c levels, irrespective of the follow-up periodontal status. This observation might be related to natural variation of HbA1c levels over time such that periodontitis patients with baseline HbA1c levels near the 5.7% threshold exhibit levels slightly above 5.7% at follow-up visits. However, for 3 patients, HbA1c levels were in the diabetic range (7% at maximum) after 27.5 mo (Figure B). Nevertheless, the majority (84.1%) remained in the normal group.

Some strengths and limitations of this study deserve consideration. Strengths include the relatively high sample size, also within subgroups of normal HbA1c and prediabetes subjects. Among the limitations, this was a secondary analysis including patient data pooled over treatment allocation. This was justified by nonsignificant effects of treatment allocation on change in HbA1c levels (Appendix Table 5) and hsCRP levels (Appendix Table 6) between baseline and follow-up visits, as indicated by the interaction terms between treatment allocation and visit. The results for hsCRP were in agreement with a previous randomized clinical trial with comparable treatment groups that reported no differences between treatment arms with regard to rates of change in CRP levels (Lopez et al. 2012). In this context, it should again be noted that randomization across groups defined by baseline HbA1c status was absent in this study. This was handled by implementation of linear mixed models with an unstructured covariance structure and comprehensive adjustments for covariates. Furthermore, linear mixed models enabled handling of records with missing data. In addition, the per-protocol and intention-to-treat samples yielded consistent results with regard to direction and size of least square mean estimates such that HbA1c levels decreased by 0.35% and 0.95% between baseline and both follow-up visits in the prediabetic and diabetic groups with either sample, respectively. Second, the absence of robust physiologic measurements limits a mechanistic interpretation of our observations. Third, information on new antidiabetic medication during the trial period was recorded not directly but through the medication change comment field (see Appendix). Thus, we cannot exclude that information on new antidiabetic medication was incomplete. Nevertheless, these comment fields indicated no new antidiabetic medication during the trial period. Thus, we assume that HbA1c reductions were not related to changes in antidiabetic medication. Fourth, intake of anti-inflammatory medication during the trial period might have affected changes in systemic inflammation and, thus, HbA1c levels. However, at any visit, a maximum of 10, 6, and 1 patients from the normal, prediabetes, and diabetes groups took acetylsalicylic acid, respectively (see Appendix). Thus, potential effects on changes in systemic inflammation and HbA1c levels may be negligible.

Last, decreasing HbA1c levels among persons with prediabetes at baseline might have occurred due to regression to the mean instead of being related to the periodontal treatment itself. On the one hand, if regression to the mean was present, a greater decrease in HbA1c levels would be more often observed for prediabetes subjects with higher baseline HbA1c levels. However, as seen in time course plots (see Figure B, prediabetes group), changes in HbA1c measurements were not related to baseline HbA1c levels, which does not support the assumption that the decreasing HbA1c levels of prediabetes subjects were related to regression to the mean. On the other hand, correlation plots of changes in mean PPD and HbA1c levels between baseline and 27.5-mo examinations support the notion that changes in HbA1c levels might have been related to periodontal treatment. Indeed, most periodontitis patients showed improvements in mean PPD and HbA1c levels, and the Spearman correlation for periodontitis patients with prediabetes was 0.17, indicating a weak but positive correlation. In addition, previous studies support the notion that the reductions seen in this study were probably due to periodontal treatment rather than regression to the mean. In randomized clinical trials that evaluated effects of periodontal treatment on metabolic control, periodontally untreated diabetes patients (controls) showed unchanged HbA1c levels (Engebretson et al. 2013; Zhang et al. 2013). Nevertheless, we cannot exclude the possibility that changes in HbA1c levels occurred due to regression to the mean, bias potentially introduced by the study design (i.e., no randomization across groups defined by baseline HbA1c status), or other causes, thereby precluding any causal interpretation of the results. Thus, our secondary analysis should rather be regarded as hypothesis generating. Only a study with a randomized double-blind design can determine whether observations seen in this study will hold true.

In summary, this exploratory subgroup analysis of the multicenter randomized controlled ABPARO trial—a prospective, stratified, double-blind study—suggests that nonsurgical periodontal treatment might reduce systemic hyperglycemia among people with prediabetes. In parallel, local periodontal inflammation and low-grade systemic inflammation decreased over the follow-up period. If one-third of patients with severe or moderate periodontitis suffer from prediabetes and if two-thirds of these benefit from nonsurgical periodontal treatment because progression toward hyperglycemia is retarded, then this basic periodontal treatment, which has no negative adverse side effects, must prove its utility in general clinical practice. To determine whether family and specialist dental practices can serve as potential health care providers for prediabetes treatment among periodontitis patients, large well-designed multicenter randomized clinical trials are required.

Author Contributions

T. Kocher, contributed to conception, design, data acquisition, and interpretation, drafted the manuscript; B. Holtfreter, contributed to data analysis and interpretation, drafted the manuscript; A. Petersmann, D. Kaner, T.S. Kim, S. Doering, M. Gravemeier, K. Prior, W. Rathmann, I. Harks, contributed to data acquisition, critically revised the manuscript; P. Eickholz, T. Hoffmann, J. Meyle, U. Schlagenhauf, B. Ehmke, contributed to conception, design, and data acquisition, critically revised the manuscript; R. Koch, contributed to data analysis and interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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Data Availability

Due to data safety regulations, data from the ABPARO trial are not freely available. On request, data extracts can be provided from the Department of Periodontology, University Hospital Münster, Münster, Germany, for researchers who meet the criteria for access to confidential data.

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References

Alshehri FA, Javed F. 2015. Impact of scaling and root planing on clinical periodontal status and glycemic levels in prediabetic patients. Interv Med Appl Sci. 7(1):17–21.

Bo A, Thomsen RW, Nielsen JS, Nicolaisen SK, Beck-Nielsen H, Rungby J, Sorensen HT, Hansen TK, Sondergaard J, Friborg S, et al. 2017. Early onset type 2 diabetes: age gradient in clinical and behavioural risk factors in 5115 persons with newly diagnosed type 2 diabetes—results from the DD2 study. Diabetes Metab Res Rev. 34(3). doi:10.1002/dmrr.2968

Centers for Disease Control and Prevention. 2014. National diabetes statistics report: estimates of diabetes and its burden in the United States. Atlanta (GA): US Department of Health and Human Services.

Chiasson JL. 2007. Prevention of type 2 diabetes: fact or fiction? Expert Opin Pharmacother. 8(18):3147–3158.

Demmer RT, Jacobs DR Jr, Desvarieux M. 2008. Periodontal disease and incident type 2 diabetes: results from the First National Health and Nutrition Examination Survey and its epidemiologic follow-up study. Diabetes Care. 31(7):1373–1379.

Demmer RT, Trinquart L, Zuk A, Fu BC, Blomkvist J, Michalowicz BS, Ravaud P, Desvarieux M. 2013. The influence of anti-infective periodontal treatment on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 8(10):e77441.

Eke PI, Dye BA, Wei L, Slade GD, Thornton-Evans GO, Borgnakke WS, Taylor GW, Page RC, Beck JD, Genco RJ. 2015. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. J Periodontol. 86(5):611–622.

Engebretson SP, Hyman LG, Michalowicz BS, Schoenfeld ER, Gelato MC, Hou W, Seaquist ER, Reddy MS, Lewis CE, Oates TW, et al. 2013. The effect of nonsurgical periodontal therapy on hemoglobin A1c levels in persons with type 2 diabetes and chronic periodontitis: a randomized clinical trial. JAMA. 310(23):2523–2532.

Eyre H, Kahn R, Robertson RM. 2004. Preventing cancer, cardiovascular disease, and diabetes: a common agenda for the American Cancer Society, the American Diabetes Association, and the American Heart Association. Diabetes Care. 27(7):1812–1824.

Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. 2012. Reduction of insulin resistance and plasma glucose level by salsalate treatment in persons with prediabetes. Endocr Pract. 18(6):826–833.

Faghihimani E, Aminorroaya A, Rezvanian H, Adibi P, Ismail-Beigi F, Amini M. 2013. Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. Acta Diabetol. 50(4):537–543.

Giannopoulou C, Cionca N, Almaghlouth A, Cancela J, Courvoisier DS, Mombelli A. 2016. Systemic biomarkers in 2-phase antibiotic periodontal treatment: a randomized clinical trial. J Dent Res. 95(3):349–355.

Goldfine AB, Fonseca V, Jablonski KA, Chen YD, Tipton L, Staten MA, Shoelson SE. 2013. Salicylate (salsalate) in patients with type 2 diabetes: a randomized trial. Ann Intern Med. 159(1):1–12.

Grossmann V, Schmitt VH, Zeller T, Panova-Noeva M, Schulz A, Laubert-Reh D, Juenger C, Schnabel RB, Abt TG, Laskowski R, et al. 2015. Profile of the immune and inflammatory response in individuals with prediabetes and type 2 diabetes. Diabetes Care. 38(7):1356–1364.

Harks I, Harmsen D, Gravemeier M, Prior K, Koch R, Doering S, Petersilka G, Weniger T, Eickholz P, Hoffmann T, et al. 2014. A concept for clinical research triggered by suggestions from systematic reviews about adjunctive antibiotics. Appl Clin Res Clin Trials Reg Aff. 1(1):43–50.

Harks I, Koch R, Eickholz P, Hoffmann T, Kim TS, Kocher T, Meyle J, Kaner D, Schlagenhauf U, Doering S, et al. 2015. Is progression of periodontitis relevantly influenced by systemic antibiotics? A clinical randomized trial. J Clin Periodontol. 42(9):832–842.

Holm NC, Belstrom D, Ostergaard JA, Schou S, Holmstrup P, Grauballe MB. 2016. Identification of individuals with undiagnosed diabetes and pre-diabetes in a Danish cohort attending dental treatment. J Periodontol. 87(4):395–402.

Javed F, Ahmed HB, Mehmood A, Bain C, Romanos GE. 2014. Effect of non-surgical periodontal therapy (with or without oral doxycycline delivery) on glycemic status and clinical periodontal parameters in patients with prediabetes: a short-term longitudinal randomized case-control study. Clin Oral Investig. 18(8):1963–1968.

Kanat M, DeFronzo RA, Abdul-Ghani MA. 2015. Treatment of prediabetes. World J Diabetes. 6(12):1207–1222.

Kerrison G, Gillis RB, Jiwani SI, Alzahrani Q, Kok S, Harding SE, Shaw I, Adams GG. 2017. The effectiveness of lifestyle adaptation for the prevention of prediabetes in adults: a systematic review. J Diabetes Res. 2017:8493145.

Koloverou E, Panagiotakos DB, Georgousopoulou EN, Chrysohoou C, Tousoulis D, Stefanadis C, Pitsavos C. 2017. Single and combined effects of inflammatory markers on 10 year diabetes incidence: the mediating role of adiposity—results from the ATTICA cohort study. Diabetes Metab Res Rev. 34(1). doi:10.1002/dmrr.2939

Konig J, Holtfreter B, Kocher T. 2010. Periodontal health in Europe: future trends based on treatment needs and the provision of periodontal services—position paper 1. Eur J Dent Educ. 14 Suppl 1:4–24.

Lalla E, Cheng B, Kunzel C, Burkett S, Ferraro A, Lamster IB. 2015. Six-month outcomes in dental patients identified with hyperglycaemia: a randomized clinical trial. J Clin Periodontol. 42(3):228–235.

Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY. 2007. Interleukin-1-receptor antagonist in type 2 diabetes mellitus. N Engl J Med. 356(15):1517–1526.

Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. 2008. Bacteremia associated with toothbrushing and dental extraction. Circulation. 117(24):3118–3125.

Loos BG, Craandijk J, Hoek FJ, Wertheim-van Dillen PM, van der Velden U. 2000. Elevation of systemic markers related to cardiovascular diseases in the peripheral blood of periodontitis patients. J Periodontol. 71(10):1528–1534.

Lopez NJ, Quintero A, Casanova PA, Ibieta CI, Baelum V, Lopez R. 2012. Effects of periodontal therapy on systemic markers of inflammation in patients with metabolic syndrome: a controlled clinical trial. J Periodontol. 83(3):267–278.

Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, Cavan D, Shaw JE, Makaroff LE. 2017. IDF diabetes atlas: global estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 128:40–50.

Perreault L, Pan Q, Mather KJ, Watson KE, Hamman RF, Kahn SE. 2012. Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study. Lancet. 379(9833):2243–2251.

Reijnders D, Goossens GH, Hermes GD, Neis EP, van der Beek CM, Most J, Holst JJ, Lenaerts K, Kootte RS, Nieuwdorp M, et al. 2016. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell Metab. 24(2):341.

Simpson TC, Weldon JC, Worthington HV, Needleman I, Wild SH, Moles DR, Stevenson B, Furness S, Iheozor-Ejiofor Z. 2015. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Cochrane Database Syst Rev. (11):CD004714.

Stuart A. 1955. A test for homogeneity of the marginal distributions in a two-way classification. Biometrika. 42(3/4):412–416.

Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. 2012. Prediabetes: a high-risk state for diabetes development. Lancet. 379(9833):2279–2290.

Verbeke G, Molenberghs G. 2000. Linear mixed models for longitudinal data. New York (NY): Springer.

Zhang H, Li C, Shang S, Luo Z. 2013. Scaling and root planing with enhanced root planing on healthcare for type 2 diabetes mellitus: a randomized controlled clinical trial. J Dent Sci. 8(3):272–280.