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Does periodontal care improve glycemic control? The Department of Veterans Affairs Dental Diabetes Study

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Abstract

Objectives: Report results of a randomized-clinical trial of the efficacy of periodontal care in the improvement of glycemic control in 165 veterans with poorly controlled diabetes over 4 months.

Methods: Outcomes were change in Haemoglobin A1c (HbA1c) in the Early Treatment *versus* untreated (Usual Care) groups and percent of participants with decreases in HbA1c. Analyses included simple/multiple variable linear/logistic regressions, adjusted for baseline HbA1c, age, and duration of diabetes.

Results: Unadjusted analyses showed no differences between groups. After adjustment for baseline HbA1c, age, and diabetes duration, the mean absolute HbA1c change in the Early Treatment group was -0.65% *versus* -0.51% in the Usual Care group ($p = 0.47$). Adjusted odds for improvement by 0.5% in the Early Treatment group was 1.67 (95% confidence interval: 0.84, 3.34, $p = 0.14$). Usual Care subjects were twice as likely to increase insulin from baseline to 4 months (20% *versus* 11%, $p = 0.12$) and less likely to decrease insulin (1% *versus* 6%, $p = 0.21$) than Early Treatment subjects. Among insulin users at baseline, more increased insulin in the Usual Care group (40% *versus* 21%, $p = 0.06$).

Conclusions: No significant benefit was found for periodontal therapy after 4 months in this study; trends in some results were in favour of periodontal treatment.

Key words: clinical trial; diabetes; glycemic control; HbA1c; periodontal disease

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Reports suggest that patients with diabetes tend to have more periodontal disease, and that hyperglycemia fosters periodontitis and its progression (Grossi & Genco 1998, Taylor 1999, 2001, 2003, U.S. Department of Health and Human Services 2000, Iacopino 2001, Amar & Han 2003, Hertz- Mayfield 2005). However, clinical data supporting the existence and strength of an effect of periodontal disease on diabetes are sparse. Some studies suggest that improvements in periodontal condition will improve glycemic control (Miller et al. 1992, Taylor et al. 1996, Grossi et al. 1997, Taylor 1999, Stewart et al. 2001, Rodrigues et al. 2003), while others have not found such a relationship (Seppala & Ainamo 1994, Aldridge et al. 1995, Smith et al. 1996, Westfelt et al. 1996, Firatli 1997, Christgau et al. 1998, Collin et al. 1998). Taylor (1999), Stewart et al. (2001), Borrell & Papapanou (2005) suggest that clinical trials are needed to determine the efficacy of periodontal care in improving glycemic control in diabetes. The purpose of this paper is to report 4-month results of a clinical trial of the efficacy of periodontal care in the improvement of glycemic control in veterans with poorly controlled diabetes.

Methods

This multi-site, single-blind, randomized, controlled clinical trial examined the efficacy of periodontal care in the improvement of glycemic control in veterans with poorly controlled diabetes at four Department of Veterans Affairs (VA) facilities in greater Boston from December 2000 until November 2004. The institutional review boards at all four facilities approved the study. All subjects gave written informed consent.

Design

The study had a two by two design (Fig. 1). In one direction, analyses examined whether a single course of periodontal therapy improved glycemic control over a 4-month period. Participants were randomized to either an ''Early Treatment'' or ''Usual Care'' group. ''By Usual Care'' we mean that the participants used did not alter their medical and dental care routine; rather, they proceeded with their health care as usual. For some this meant that they used dental and medical services, for others it did not. After 4 months of initial treatment, half of each group was randomized to return to their Usual Care and the other half to continued structured periodontal therapy in the study for 12 months. This paper reports on data from the first 4 months.

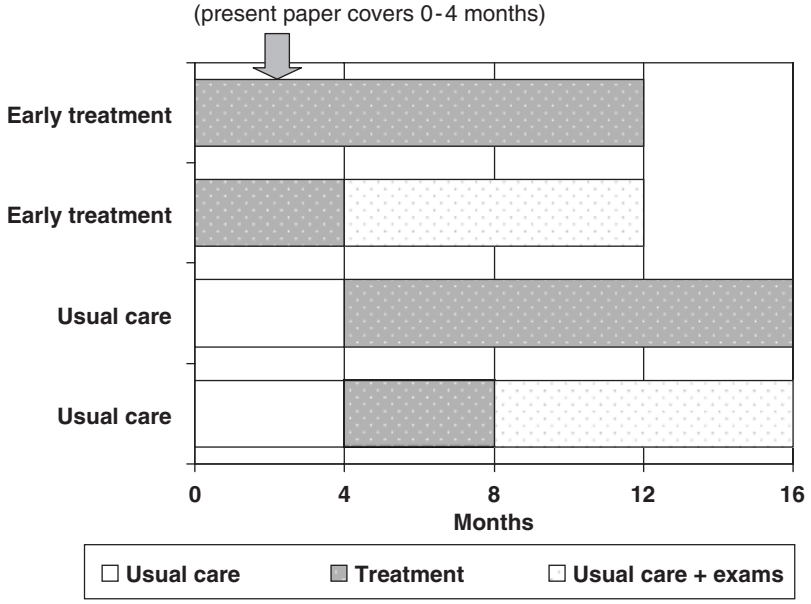

Fig. 1. Study design: Department of Veterans Affairs Dental Diabetes Study.

Identification and recruitment

Potential subjects were veterans with one or more Haemoglobin A1c (HbA1c) values $>8.5\%$ within the last 6 months. We contacted primary care providers to obtain their concurrence with our contacting their patients for potential inclusion in the study. Once obtained, we sent a letter to the veteran describing the study and inviting participation. Veterans indicated interest (yes/no) using a pre-addressed, postage-paid postcard. If the postcard was not returned, the letter informed the veteran that s/he would be contacted in 2 weeks. After 2 weeks, we called veterans to determine interest and to screen for eligibility using a standardized script. Interested veterans were asked to return for a blood test to confirm poor glycemic control.

Inclusion and exclusion criteria

Interested veterans with a repeat HbA1c $\geqslant 8.5\%$ were eligible for inclusion; while arguments could be made for any level between 7% and 10%, 8.5% was chosen because it clearly left room for improvement but included a broad range of poor control. Further, veterans were eligible for inclusion if they used VA outpatient care, were willing to participate in a 12–16-month study, had at least eight teeth, and had sufficient periodontal treatment need as indicated by Community Periodontal Index of Treatment Need (CPITN; Ainamo et al. 1982) scores of $\geqslant 3$ in at least two sextants. Exclusion criteria included malignancy, immune compromise (e.g. post-organ transplant, HIV), or poor health. Veterans were also excluded if there was exudate on probing or palpation until acute infection was eliminated.

Randomization

Eligible/interested veterans were randomized into four study groups using a stratified schema (Fig. 1):

1. *Early Treatment/4 months therapy*: Early Treatment for 4 months (periodontal scaling and root planing until smooth root surfaces were achieved plus doxycycline [100 mg by mouth daily for 14 days] and chlorhexidine gluconate [CHX] rinses [30 cc, 0.12%, twice daily for 4 months]), then Usual Care.
2. *Early Treatment/12 months therapy*: Early Treatment, continued for 12 months. Participants were seen every 4 months for periodontal scaling and root planing. No additional antimicrobials were used.
3. *Usual Care/4 months therapy*: Usual Care, then 4 months of treatment, then Usual Care.
4. *Usual Care/12 months therapy*: Usual Care, then 12 months of treatment as in #2.

We stratified by site (Boston *versus* Providence *versus* [Manchester+Bedford]) because we expected recruitment to be different in each site and because the populations have varying frequencies of minority and low-income veterans. We used *proc plan* in SAS (Statistical Analysis Systems, Cary, NC, *Version 8.1)* to obtain 12 blocks of eight, using a seed of 020348. The resulting group assignments were put on white cards, sealed in white envelopes, and numbered consecutively. Study staff took the top envelope from the strata's pile to assign study group.

Masking

The study examiner (C. J. W.) did not know to which study group participants were assigned; participants were aware of whether they received care immediately or after 4 months, and whether care continued for 4 or 12 months.

Study procedures

Once participants were randomized, each received a detailed chart review by the principal investigator (J. A. J.) to assess health status, determine the need for pre-medication for periodontal probing and therapy, and to confirm eligibility. Subjects not meeting eligibility criteria were excluded at this stage.

Outcomes of interest

HbA1c data were obtained from the VA Computerized Patient Record System; 100% were verified for accuracy and

performed at the same laboratory (Boston VA Healthcare System, West Roxbury Division Clinical Laboratory, Boson, MA, USA). Change in HbA1c from baseline to 4 months was the primary outcome of interest. This was analysed as a continuous variable and as the percent of participants with improvements of 0.5% and 1.0% in HbA1c (chosen because they represent clinically important improvements associated with decreases in diabetes-associated morbidity and mortality, The Diabetes Control and Complications Trial Research Group 1993, UKPDS 1998, United Kingdom Prospective Diabetes Study Group 1998).

Baseline Measures

We obtained data on age, pre-study HbA1c, and comorbid medical conditions from the computerized VA outpatient clinic file (OPC). We used data from outpatient visits for the 3 years before the baseline HbA1c and listed all unique diagnoses of co-morbid medical conditions. From the lists of diagnoses, we calculated the comorbidity index (CMI; Selim et al. 2004) and the diabetes-related comorbidity index (DBI; Personal communication, drmiller@bu.edu). Clinical examination data on number of teeth, periodontal treatment need (CPITN; Ainamo et al. 1982), gingival index (Löe et al. 1967), gingival recession (in millimetres, six sites per tooth), pocket depth (in mm, six sites per tooth, measured twice), and presence of exudate on palpation and probing were collected at baseline in the Early Treatment group and at the initial examination done at month 4 (their clinical baseline) in the Usual Care group. The percent following the protocol (time between baseline and 4-month visit = 121 ± 60 days) was also collected. Self-reported questionnaire data were used for race, sex, smoking status, body mass index (weight in kilogram/[height in metres]^2), duration of diabetes, oral, and general health, stress, activity level in kilojoules (kJ/day), alcoholic drinks per week, and diabetes medicines (insulin and oral medications).

Data management and analyses

Clinical data were entered chair-side into a laptop data entry system. Questionnaire data were double entered and verified for accuracy. All analyses were conducted in Statistical Analysis Systems (SAS) *Versions 8.02 and 9.1* (Cary, NC, USA) and based on intention to treat. The χ^2 statistic tested for between-group differences in frequencies of baseline characteristics and proportion of subjects with 0.5% and 1% changes in HbA1c over the initial 4-month period. *T*-tests were used to test for differences in baseline means and mean changes in HbA1c. Multiple variable linear/logistic regression analyses were conducted regressing change in HbA1c on study group and relevant covariates. If 4-month data for weight, activity, and diabetes medications were missing, we carried forward baseline values. This did not substantially change the results. Candidate explanatory variables for final regressions included items that were different by study group at baseline or were related to the outcome at $p = 0.20$, and clinically important potential confounders that changed the main effect (determined by the *t*-statistic). Multiple variable logistic regression analyses were conducted regressing decreases of 0.5% and 1% in HbA1c on study group and these same covariates. We used $p < 0.05$ as a cutoff for statistical significance and $p < 0.1$ to indicate trends.

A priori power analysis

The study was designed to have 300 participants. Allowing for 33% attrition, we expected 200 patients studied, 100/group. We anticipated 80% power to detect a moderate-sized effect (ES $\delta = 0.40$) of the intervention in two-sided tests at the 5% level. For the analysis at 4 months comparing the proportion of patients in Early Treatment and Usual Care groups who experienced a greater than 1% drop in their HbA1c levels, we expected similar power.

Results

We recruited 193 participants with HbA1c $\geqslant$8.5%. Details of the comparison between the randomized and non-randomized are published elsewhere (Jones et al. 2006). Briefly, in comparison with the sample frame, participants were younger, but with slightly higher HbA1cs and slightly higher prevalences of obesity, post-traumatic stress disorder, depression, and bipolar illness. Twenty-eight participants were excluded after randomization, as shown in Fig. 2. There were no significant differences in the number of exclusions by study group (12 in the Usual Care group and 16 in the Early Treatment group). Excluded participants had slightly higher baseline HbA1c values in comparison to those not excluded (10.5% *versus* 10.0%), and slightly higher DBI (3.3 *versus* 2.6). Participants in the Usual Care group who were excluded had slightly higher initial HbA1c values (10.37% *versus* 10.23%) while in the treatment group, those excluded had higher initial HbA1c values (10.5% *versus* 9.9%, $p = 0.07$).

Baseline and 4-month characteristics by study group are shown in Table 1. Participants in the Usual Care group were less likely to be current smokers and more likely to follow the strict timeline of the protocol. Veterans in the Usual Care group were twice as likely (20% *versus* 11%, $p = 0.12$) to increase insulin from baseline to 4 months and less likely to decrease insulin (1% *versus* 6%, $p = 0.21$).

Bivariate relationships between baseline and 4-month characteristics and improvements (decreases) in HbA1c of at least 0.5% and 1% showed strong associations between baseline HbA1c, adherence to the time course of the protocol, a history of depression and anxiety, and diabetes medications at baseline (data not shown).

The results of regression analyses are shown in Table 2. Simple and multiple variable linear regressions showed no differences between groups in HbA1c change for either the unadjusted or adjusted analyses (-0.63% *versus* -0.61%, p = NS unadjusted, -0.51% *versus* -0.65%, p = NS, adjusted for baseline HbA1c, age $\geqslant$55, and diabetes duration).

The unadjusted percent with improvements in 0.5% and 1% showed no significant differences by group. After adjustment for baseline HbA1c, age $\geqslant$55, and duration of diabetes, multiple variable logistic regressions showed that the estimated odds ratio for improvement by 0.5% in the Early Treatment group was 1.67 (95% confidence interval [CI]: 0.84, 3.34, $p = 0.14$) while the odds ratio for improvement by 1% was 1.67 (95% CI: 0.81, 3.44, $p = 0.16$). Adjustments for improvement in the percent of sites with pockets depths >3 mm attenuated the main effect.

Compliance with medications

Compliance with the study drug regimen was not universal. Eighty-three

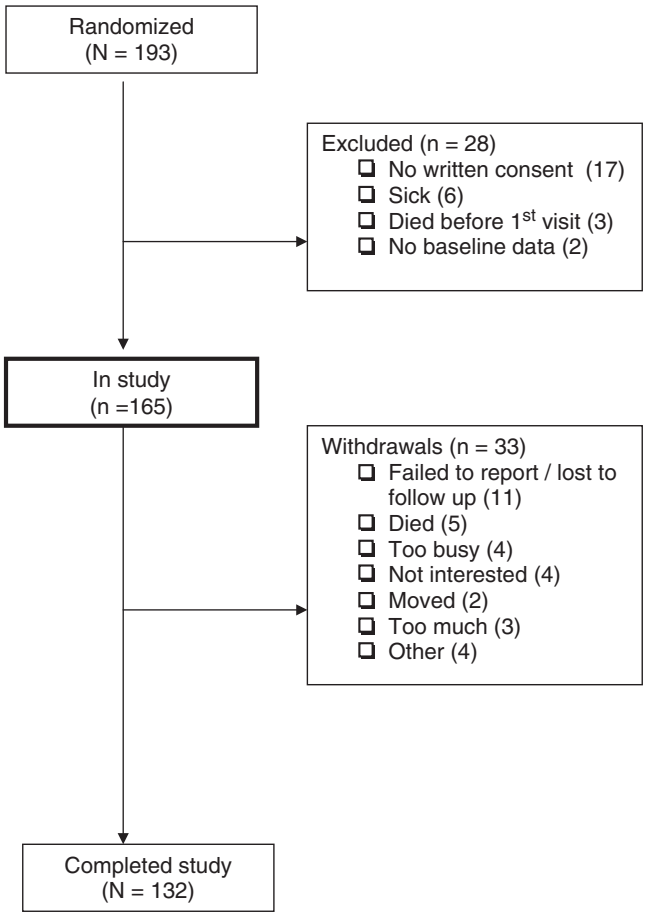

Fig. 2. Exclusions and withdrawals: Department of Veterans Affairs Dental Diabetes Study.

percent used both chlorhexidine and doxycycline, another 8% used chlorhexidine only, and 7% used doxycycline only. Thus, over 90% in the treatment group used each study drug. Among users of chlorhexidine, 17 participants reported less than daily use, 19 reported daily use, and 29 reported twice daily use. One chlorhexidine user had four bottles left, nine had two to three bottles left, 16 had one left, and 41 used all the chlorhexidine. Among doxycycline users 50 reported using all the pills, two had <10 pills left (of 14), and five had more than 10 pills left.

Adverse events

The most commonly reported symptoms among veterans taking doxycycline were gastrointestinal: diarrhea (7.1%), abdominal pain (3.6%), and nausea (2.9%). Among subjects using chlorhexidine, the most common symptoms were changes in taste (15.0%), tooth staining (13.6%), and sore mouth or tongue tip irritation (5.0% each). Swelling of the face, lips, and throat and shortness of breath were also reported.

Discussion

The data presented do not provide statistically significant evidence of a treatment effect during the 4-month period of this trial. However, some analyses show a trend in favour of periodontal therapy. Subjects who received periodontal therapy were more likely to achieve reductions in HbA1c of 0.5% and 1% (although results were not statistically significant at the 0.05 level), and were less likely to receive increases in insulin (Table 1). While the mean changes in HbA1c were not significantly different by study group, differences in adjusted analyses were on the order of 0.14%. With a standard deviation of 1.31, the effect size was small (0.14/1.3), is 0.11. Thus, to detect a statistically significant difference with this effect size, we would have needed 1376 participants per group. If the study outcome is proportion with improvements of HbA1c of at least 1%, to detect a 10% difference in this proportion, sample sizes would need to be 630 per group using an unadjusted model and 362 per group using an adjusted model.

Elimination of periodontal infection, healing of deepened periodontal pockets, and maintenance of a healthy periodontium are the goals of periodontal therapy. As suggested by the work of Rodrigues et al. (2003) and Grossi et al. (1997), it is possible that the incomplete healing in our study contributed to the lack of a difference between the two groups. Note, that with an average of 21 teeth, with six sites per tooth examined, there was a mean of 126 examined surfaces/subject. At baseline, >3 mm deep pockets were detected on 13.9% of the sites in the Early Treatment group (and on 13.6% in the Usual Care group), i.e., a mean of ~ 18 sites per person. Similarly, there were, on average, $3>5$ mm sites per person. After 4 months, and after therapy in the Early Treatment group, a mean of 10 of the original $18>3$ mm pockets and two of the $3>5$ mm pockets remained. Moreover, these figures suggest that the severity of periodontal disease is not extremely high. Thus, because the healing is not complete and the infection is remaining in a number of sites (in more than half of the original sites), it is possible that further differences might be observed over a longer period of time (e.g. 12 months), especially in participants with more severe disease. Thus, in our subsequent work, we will examine healing after 12 *versus* 4 months of treatment.

A strength of this study is that it is the first, modest-sized, randomized, single-blind-controlled clinical trial to determine the efficacy of periodontal therapy in the improvement in glycemic control in diabetes; however, failure of randomization required us to control for baseline HbA1c. Previous studies have either utilized participants as their own controls (Seppala & Ainamo 1994, Smith et al. 1996, Iwamoto et al. 2001) or used groups with selection bias (Stewart et al. 2001) to examine the impact of periodontal therapy on diabetes control. We used a group receiving their usual medical and dental care for 4 months to be able to test whether the addition of periodontal therapy increased the likelihood that HbA1c would be improved.

Another strength of this study was that the use of large VA administrative

Table 1. Baseline and 4-month characteristics by study group

Characteristic	*N*	Overall mean (SD/%)	Usual TX	Early TX	Test statistics	*p*-value
Baseline						
Overall (*N*)	165		83	82		
Age	165	59.1 (11)	60	59	$t = 0.6$	0.55
Sex (% male)	165	97%	94%	100%	$x^2 = 5.1$	0.06
Race (% white)	159	81%	78%	84%	$x^2 = 0.72$	0.40
Married (%)	161	52%	56%	49%	$x^2 = 0.75$	0.39
Smoking (%):						
Current	156	24%	19%	29%	$x^2 = 8.4$	0.02
Former		54%	50%	58%		
Never		22%	31%	13%		
Baseline HbA1c	165	10.0 (1.3)	10.2	9.9	$t = 1.63$	0.11
BMI (Self-report)	161	32.1(6.5)	31.4	32.8	$t = -1.36$	0.18
Duration of diabetes (in years)	154	12.8 (9.7)	14.1	11.4	$t = 1.7$	0.09
Stress*	160	5.2 (2.6)	5.6	4.8	$t = 1.8$	0.07
CMI (Selim Comorbidity Index)	165	6 (3.4)	6.1	5.9	$t = 0.27$	0.78
DBI (Diabetes Burden Index)	165	2.6 (1.8)	2.7	2.6	$t = 0.52$	0.60
Weekly activity (kJ)	155	1863 (3003)	2079	1657	$t = 0.9$	0.38
Drinks per week	161	1.8(5)	1.43	2.2	$t = -1.0$	0.33
Dental visit within 1 year (%)	160	54.4%	59%	49%	$x^2 = 1.6$	0.21
Diabetes medicines:						
Insulin only	161	29.2%	26%	32%	$x^2 = 0.89$	0.64
Insulin & oral medicines		23.0%	25%	21%		
Oral medicines only		47.8%	49%	46%		
Took CHX & doxycycline	79	NA	NA	82%	NA	NA
N teeth	157	21(6)	21.4‡	20.7	$t = 0.78$	0.44
Gingival index	157	0.76 (0.5)	0.74‡	0.77	$t = -0.32$	0.75
CPITN (mean)	157	2.84 (0.7)	2.8‡	2.9	$t = -0.64$	0.52
Sextants w/CPITN = 3 or 4 (%)	157	61.2 (25)	60.1	62.2	$t = -0.52$	0.61
Recession (mm)	154	0.7 (0.7)	0.6‡	0.8	$t = -1.09$	0.28
Sites (w/pkts) >3 mm (%)	154	13.7 (15.6)	13.6	13.9	$t = -0.14$	0.89
Sites (w/pkts) >5 mm (%)	154	2.6 (5.6)	2.5	2.7	$t = -0.23$	0.82
Mean pocket depth (mm)	154	2.5 (0.6)	2.4‡	2.5	$t = -0.18$	0.86
Four-month parameters (baseline to 4 months)						
Compliant w/study timeframe†	165	84%	86%	82%	$x^2 = 0.44$	0.51
Percent with a dental visit (excluding dental study)	143	38%	39%	38%	$x^2 = .06$	0.81
Decrease HbA1c >0.5	165	55%	52%	55%	$x^2 = 0.76$	0.38
Decrease HbA1c >1.0	165	38%	34%	41%	$x^2 = 1.0$	0.31
Sites (w/pkts) >3 mm (%)	154	10.8 (14.4)	NA	8.1	NA	NA
Sites (w/pkts) >5 mm (%)	154	2.0 (4.8)	NA	1.6	NA	NA
Increase insulin by $\geqslant 15\%$	159	16%	20%	11%	$x^2 = 2.4$	0.12
Decrease insulin by $\geqslant 15\%$	159	4 %	1%	6%	$x^2 = 2.7$	0.21

*Patients were asked to report stress on a scale from 1 to 10, where 1, very low and 10, very high stress.

†Patients seen within 60 days of target date (62–181 days from baseline).

‡Baseline dental parameters collected at initial exam done at 4 months in ''Usual care'' group.

Only 154–157 had complete periodontal evaluations. After exclusions, eight of the initial 165 subsequently withdrew, and three persons, when examined, did not meet our entry criteria; thus they were excluded after their baseline CPITN. The missing data are reflected in Table 1.

CHX, chlorhexidine gluconate; CPITN, community periodontal index of periodontal treatment need; SD, standard deviation.

databases allowed development of risk-adjustment for comorbid diabetes-related and other medical conditions. However, preliminary models showed that risk-adjustment did not modify the main effect.

The findings in this trial are more modest than Stewart et al. (2001) who found a larger difference in mean change in HbA1c. That study, however, had significant selection bias. Nevertheless, our results support the notion of a biologic connection between periodontal disease and diabetes, first described by Williams & Mahan (1960) who found that patients with poorly controlled diabetes required less insulin after treatment of periodontal infection with extractions and antibiotics. Grossi & Genco (1998) postulated a ''self-feeding 2-way system of catabolic response resulting in more severe periodontal disease and increased difficulty controlling blood sugar''. They, along with Amar & Han (2003), suggest that up-regulation of proinflammatory cytokines, tumour necrosis factor-α (TNFα), interleukin-1 (IL-1) and IL-6 in periodontal disease may be responsible for insulin resistance and poor glycemic control. More recent evidence for a TNFα connection comes from Iwamoto et al. (2001), and Nishimura et al. (2003), who showed that periodontal therapy combined with local application of minocycline in deep pockets weekly, over 4 weeks, is related to highly correlated decreases in both TNFα and HbA1c, and decreased insulin resistance.

A potential contributing factor in regard to the study's non-significant results is that, by seeking physician

Table 2. Unadjusted and adjusted analyses of main effects

Analysis		Mean change in HbA1c		*p*-value	*C*-statistic
		usual care	early treatment		
OLS regression					
$N = 165$	Unadjusted	− 0.63%	− 0.61%	NS	
$n = 154$	Adjusted*	− 0.51%	− 0.65%	NS	
		Odds ratio	95% CI		
Logistic ($N = 165$)	Unadjusted				
	0.5% decrease	1.31	0.71, 2.43	NS	0.534
	1.0% decrease	1.39	0.74, 2.62	NS	0.541
		Odds ratio	95% CI		
Logistic $n = 154$)	Adjusted*				
	0.5% decrease	1.67	0.84, 3.34	0.14	0.658
	1.0% decrease	1.67	0.81, 3.44	0.16	0.695

*Adjusted for baseline HbA1c, duration of diabetes and age $\geqslant 55$.
CI, confidence interval; NS, not significant.

concurrence, in essence we notified each participant's primary care provider that his or her patient's diabetes was under poor control. Because of this notification, some providers likely became more aggressive in treating these patients, biasing the results towards the null. Evidence for this is the fact that among participants who used insulin at baseline ($n = 83$ overall, 43 in the Early Treatment group and 40 in the Usual Care group), a higher percent of the Usual Care group (40%) compared with the Early Treatment group (21%) had increases in insulin ($\chi^2 = 3.58$, $p = 0.06$).

This study has several important limitations. First, because of the nature of VA patients, there are few women in this study. This is an important omission that should be addressed in future trials. Second, glycemic control is a complex issue. Through randomization, we attempted to eliminate bias, and controlled for important confounders in our analyses; yet, we may have missed important variables. Third, this study was underpowered. Future study designs can take into consideration our experiences with regard to recruitment.

Conclusions

The results of this single-blind, randomized, controlled clinical trial suggest that the addition of periodontal therapy to current medical therapy may have promise in regard to improvement of glycemic control. Large-scale, multi-site, randomized clinical trials, including measurements of inflammatory mediators, are needed to definitively test the hypotheses that periodontal therapy improves glycemic control in persons with poorly controlled diabetes.

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Clinical Relevance

Scientific rationale: A Single-blind, randomized controlled trial (RCT) tested the efficacy of periodontal care on glycemic control in veterans with poorly controlled diabetes.
Principal findings: No significant clinical benefit was found for periodontal therapy after four months in this study; trends in some results favored treatment, including reductions in HbA1c of 0.5% and 1%, as well as more common decreases in insulin among users of insulin at baseline.
Practical implication: Large RCTs are needed to discern the impact of periodontal care on diabetes. Studies must include analyses of changes in medications and inflammatory mediators.