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Effect of antimicrobial periodontal treatment and maintenance on serum adiponectin in type 2 diabetes mellitus

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Abstract

Aims: The aims of this study were to evaluate the effect of mechanical periodontal treatment with local application of minocycline (APT) on serum adiponectin as a marker of insulin resistance improvement in type 2 diabetes mellitus (T2DM) patients and to investigate if effect of APT on serum adiponectin level was sustained by periodontal maintenance (PM).

Material and Methods: Twenty-seven T2DM patients were randomly assigned into test or control groups. Test received scaling with ultrasonic devices at baseline and APT biweekly for 2 months while control received scaling at baseline and mechanical tooth cleaning (MPT) at the same interval. At 6 months, all patients received mechanical tooth cleaning as PM. Periodontal examination and blood measurements were performed at baseline, 4 and 9 months.

Results: Adiponectin concentrations in test had significantly increased by 31.4% after APT ($p = 0.024$) and by 30.4% after PM ($p = 0.002$) compared with baseline. The percentage of $\geqslant 4$ mm probing depths (PD) had shown 8.3% and 9.3% reduction after APT and PM ($p = 0.046$, 0.02) in test while 5.0% reduction after MPT in control group ($p = 0.031$).

Conclusions: Our results suggested that APT and PM not only improve periodontal disease but also increase serum adiponectin in T2DM patients.

Key words: adiponectin; antimicrobial periodontal treatment; insulin resistance; periodontal disease; periodontal maintenance; randomized controlled trial; type 2 diabetes mellitus

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Periodontal infection has been implicated as a risk factor for systemic diseases such as coronary heart disease and type 2 diabetes mellitus (T2DM) (Genco et al. 2001, Nishimura et al. 2003, Jansson et al. 2006). Patients with T2DM generally have more severe periodontal disease levels compared with non-diabetic individuals (Lu & Yang 2004). On the other hand, periodontal disease has often affected diabetic status, especially in poorly controlled T2DM patients (Campus et al. 2005).

Several epidemiological studies have demonstrated that periodontal treatment with an antimicrobial agent such as minocycline and doxycycline as adjunctive to scaling and root planing is more effective than periodontal treatment alone in improving periodontal status (Williams et al. 2001, Paquette et al. 2003) as well as HbA1c level in T2DM patients (Grossi et al. 1997). Additional effects of repeated local antimicrobial administration in short-term have a potential beyond mechanical periodontal treatment in the patients with periodontal disease (van Steenberghe et al. 1993). Furthermore according to Iwamoto et al. (2001), APT which used local antimicrobial application of minocycline, was also significantly effective in reducing serum tumour necrosis factor-alpha (TNF-α), C-reactive protein (CRP), fasting insulin level and homeostasis model assessment-insulin resistance index in T2DM patients. This study suggested that APT induced periodontal improvement in T2DM patients

Conflict of interest and source of funding statement

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may be mediated by alterations in systemic inflammation as well as insulin resistance.

It has been reported that T2DM patients have relatively lower plasma adiponectin concentration compared with non-T2DM Caucasians, Pima Indians (Weyer et al. 2001) and Japanese (Hotta et al. 2000). Adiponectin is a cytokine exclusively produced by adipose tissue (Hotta et al. 2000, Wolf 2003, Wang et al. 2004, Kadowaki et al. 2006, Kim et al. 2006, Whitehead et al. 2006), which is considered to have anti-inflammatory properties (Ouchi et al. 2003). Serum adiponectin has been shown to play an important role in insulin sensitivity (Kadowaki et al. 2003, Kim et al. 2006) and to negatively related to inflammation makers such as TNF-α and CRP (Kriketos et al. 2004, Schulze et al. 2004, Shetty et al. 2004, Whitehead et al. 2006). Serum adiponectin mainly causes the improvement of insulin resistance thorough the suppression of the TNF-α – in other words, suppression of systemic inflammation. Therefore, adiponectin may be considered as an appropriate marker to assess the degree of improvement of insulin resistance in T2DM.

However, few studies have demonstrated the effect of APT by evaluating adiponectin concentration as a marker of the improvement in insulin resistance in T2DM patients (Iwamoto et al. 2003). Moreover, the effect of APT on adiponectin as well as periodontal status has been investigated at a single time point only after the treatment in T2DM patients (Iwamoto et al. 2001, 2003, Rodrigues et al. 2003, Promsudthi et al 2005). It is still uncertain the long-term effects of APT on adiponectin level if periodontal maintenance (PM) is performed after APT.

Consequently, the aim of this study was to evaluate the effect of APT, which was expected to achieve through the additional effect of minocycline to mechanical periodontal treatment, on serum adiponectin concentration as a marker of insulin resistance improvement in T2DM patients. In addition, this study also investigated the long-term effect of APT on serum adiponectin level in T2DM patients while sustaining PM.

Material and Methods

Study population

Informed consent

The subjects in this study were recruited from the out patients at the Department of Endocrinology, Niigata University Medical and Dental Hospital from August 2004 to December 2005. Informed written consent was obtained from all subjects after the screening. Before obtaining consent, the information on the safety and potential efficacy of local administration of minocycline, and the probability of receiving minocycline locally, was also explained.

Inclusion criteria

The subjects were screened for inclusion according to the following medical criteria:

(1) Minimum age of 35 years.
(2) T2DM with glycated haemoglobin (HbA1c) values 5.5% or more.
(3) No change in courses of treatment, i.e., there was no change in oral anti-diabetic drug 3 months before and during the study.
(4) No utilization of insulin injection.

T2DM was diagnosed based on the clinical criteria which were recommended by Japan Diabetes Society in 1999 (The Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus, 1999). Accordingly, T2DM is defined as the presence of a fasting plasma glucose (FPG) level of 126 mg/dl or higher, and/or the presence of a plasma glucose level of 200 mg/dl or higher, 2 h after 75 g glucose load. The existence of a casual plasma glucose level higher than 200 mg/dl is also regarded indicating T2DM. The diagnosis of T2DM is confirmed when the above criteria are met on more than two occasions, examined on separate days.

After medical screening, the subjects were screened for periodontal status according to the following criteria:

(1) At least 10 teeth present in the oral cavity.
(2) At least 10 sites with PD 4 mm or more.
(3) No periodontal treatment received 3 months before the study.

Randomization

A total of 27 patients was enrolled into this study and allocated ID numbers in the order of approval of their participant registration. After the approval, the patients who had odd ID numbers were assigned to the test group while those who had even ID numbers were assigned to the control group. The examiner was unaware whether the patients were in the test or control group while performing examinations.

Baseline characteristics

We obtained information on age, sex, body mass index (BMI) and HbA1c at baseline from medical records in the computerized medical care information system in Niigata University Medical and Dental Hospital. The information on smoking and alcohol intake was also taken by a self-administered questionnaire.

Clinical procedures

The patients in test group received scaling with ultrasonic device (Odontoson®, Yoshida Dental Trade Distribution Co., Ltd., Tokyo, Japan) to remove subgingival plaque and calculus at baseline and mechanical tooth cleaning and antimicrobial agent (APT) to remove supragingival plaque with oral hygiene instructions biweekly over 2 months. Antimicrobial agent, 2% minocycline hydrochloride gel, was applied along the gingival margin with a specially designed applicator that contained minocycline hydrochloride equivalent to 10 mg minocycline in 0.5 g ointment (PERIOFEEL DENTAL Oint. 2%®, Showa Yakuhin Kako Co., Ltd., Tokyo, Japan). Minocycline hydrochloride gel was repeatedly inserted into every site with PD of 4 mm or more. On the other hand, the patients in control group received scaling with ultrasonic device at baseline and mechanical tooth cleaning (MPT) biweekly for two months. At 6 months after baseline, all patients in both groups received PM in the form of mechanical tooth cleaning to remove supragingival plaque and oral hygiene instructions.

Clinical measurements

Periodontal examination was conducted at the Division of Preventive Dentistry, Niigata University Medical and Dental Hospital. All investigations were performed by one examiner using mouth mirrors and WHO CPI Probes (Perio probe WHO®, YDM Co., Ltd., Tokyo, Japan) under artificial light. Periodontal condition, measured as PD, was recorded at baseline, at 4 months (2 months after APT/MPT) and 9 months (3 months after PM). Probing was performed at six sites per tooth for all teeth present, and the

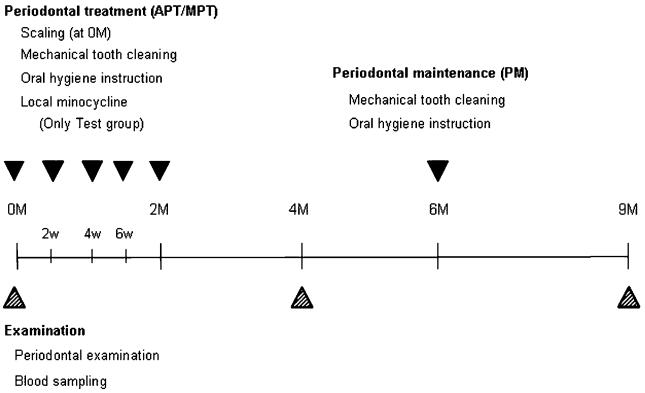

Fig. 1. Clinical procedures of this study.

measurements were recorded approximately to the nearest whole millimetres. The patients and examiners were not informed if the subjects were given the test treatment or control treatment, however, administrators of periodontal treatment knew therapeutic regimen. Figure 1 explains the outline of the procedures conducted at each appointment.

Blood sampling and laboratory analyses

A fasting blood sample was taken before periodontal examination and conducting periodontal procedures at baseline, at 2 months after APT/MPT and at 3 months after PM. Blood samples were assayed for serum levels of adiponectin, TNF-α and hs-CRP. Serum adiponectin and TNF-α concentrations were assayed by Enzymeimmunoassay and serum hs-CRP was assayed by latex Nepherometry method. These assays were ordered and performed by the commercial medical laboratory (BML Inc., Tokyo, Japan).

Statistical analysis

Initially, Student's *t*-test was used to determine the attributions and differences between the two groups at baseline for adiponectin, TNF-α, hs-CRP and the percentage of sites with $\geqslant$4 mm PD because the analysis of these data revealed a normal distribution with Kolmogorov–Smirnov test. Fisher's exact test was similarly used for categorical variables including gender, BMI, habits of smoking and alcohol.

The effects of APT/MPT and PM on adiponectin, TNF-α, hs-CRP the percentage of sites with $\geqslant$4 mm PD and HbA1c in each group were determined using the repeated measures ANOVA. If this analysis revealed significant differences among the values at baseline, 2 months after APT/MPT and 3 months after PM, post hoc analyses were performed by means of multiple comparisons with Fisher's LSD.

The statistical significance of the differences in adiponectin, TNF-α, hs-CRP, the percentage of sites with $\geqslant$4 mm PD and HbA1c between two groups at baseline and 2 months after APT/MPT and 3 months after PM were analyzed using Student's *t*-test. Pearson's correlation technique was used to evaluate the pair-wise relationships between serum levels of adiponectin, TNF-α, hs-CRP, the percentage of sites with $\geqslant$4 mm PD and HbA1c at 2 months after APT/MPT and at 3 months after PM in both test and control groups. *p*-Values of <0.05 were considered to represent statistical significance. All calculations and statistical analyses were performed using the SPSS 16.0® software package (SPSS Japan Inc., Tokyo, Japan).

Results

Out of 27 patients who were enrolled into this study six were excluded from analysis because of the following reasons. It was not able to record serum blood measurements of two patients at baseline while of another at 3 months after PM in test group. In control group, serum blood measurement was not carried out in one patient at baseline and in another at 2 months after MPT. In addition, one patient in control group who had undergone a surgery for fracture of the femur reduction during the study was also excluded from analysis. Table 1 shows subject characteristics at baseline by test and control groups. Mean age of test group was 61.5 ± 7.9 years and that of control group was 56.4 ± 7.0 years. Thirty-six percent of subjects in test group and 50% in control group showed adiponectin levels of $\leqslant$7.0 μg/ml. The distribution of serum TNF-α ranged from 12 to 36 pg/ml in test group and from 13 to 31 pg/ml in control group. Three subjects in test group and two subjects in control group showed higher levels of hs-CRP, which were 0.1 mg/dl and more. The mean HbA1c levels were 7.1 ± 0.9% in test group and 7.4 ± 1.1% in control group. The distribution of BMI was 18.9–25.9 in test group and 20.2–26.4 in control group, respectively. There were no significant differences between the two groups in relation to age, gender, smoking, alcohol, adiponectin, TNF-α, hs-CRP and HbA1c. The mean number of sites with $\geqslant$4 mm PD in test group was significantly higher than that in control group ($p = 0.005$).

Figure 2 shows the distribution of serum adiponectin in both groups at baseline, 2 months after APT/MPT and 3 months after PM. In test group, the mean level of adiponectin had significantly increased by 31.4% at 2 months after APT a compared with baseline level ($p = 0.024$). At 3 months after PM the concentration of adiponectin was significantly higher than that at baseline by 30.4% ($p = 0.002$).

The distribution of the percentage of sites with $\geqslant$4 mm PD at baseline, 2 months after APT/MPT and 3 months after PM in both groups is shown in Fig. 3. The percentage of sites with $\geqslant$4 mm PD in test group had been significantly reduced by 8.3% at 2 months after APT ($p = 0.046$) and 9.3% at 3 months after PM ($p = 0.020$), respectively, from baseline. On the other hand, sites with $\geqslant$4 mm PD in control group had been significantly reduced by 5.0% at 2 months after MPT ($p = 0.031$). Although the percentage of sites with $\geqslant$4 mm PD in this group at 3 months after PM was reduced by 4.5% compared with baseline, no significant difference was detected.

The mean TNF-α concentration showed a slight increase (16.0%) at 2 months after APT while it decreased throughout PM. After APT, the mean hs-CRP decreased from 0.102 to 0.087 mg/dl whereas at 3 months after PM it remained at a lower concentration compared with baseline level. However, none of these changes were statistically significant. On the other hand, there were no significant changes in relation

Table 1

Group	Age	Gender	Smoking	Alcohol drinking	BMI (kg/m^2)	Adiponectin (μg/ml)	TNF-α (pg/ml)	hs-CRP (mg/dl)	Sites with ≥ 4 mm PD (%)	HbAlc (%)
Test	55	M			23.3	10.9	15	0.029	34.7	8.3
	61	F	Y	N	20.3	11.5	19	0.041	16.7	6.5
	54	M	Y	Y	21.5	6.8	15	0.038	26.9	7.5
	68	F	Y	N	25.9	17.7	12	0.011	20.4	6.3
	46	M	F	N	23.5	5.3	26	0.406	12.2	7.6
	67	M	N	N	23.0	3.4	22	0.320	71.2	8.7
	65	M	F	N	24.1	9.2	17	0.036	44.2	6.6
	72	M	F	N	22.5	6.3	26	0.038	24.7	5.5
	52	M	Y	N	18.9	19.7	14	0.030	35.1	7.5
	63	M	N	Y	24.8	11.2	36	0.153	29.3	6.7
	63	M	F	N	22.9	9.0	28	0.020	14.4	6.6
Control	57	M	N	N	21.7	13.2	16	0.012	7.4	7.1
	51	M	F	N	20.2	6.1	20	0.116	19.1	6.4
	66	F	N	N	24.6	5.2	13	0.177	8.6	8.4
	56	M			20.6	11.8	14	0.005	10.7	8.1
	65	M	N	Y	26.4	3.8	20	0.043	22.0	6.6
	42	M	Y	Y	22.5	7.5	17	0.089	15.4	8.7
	61	F	N	Y		11.7	16	0.012	12.5	6.9
	56	M	F	Y	25.5	6.6	18	0.013	12.4	6.6
	52	M	Y	N	28.6	4.7	31	0.081	6.5	9.5
	58	F	N	N		8.9	22	0.087	5.4	7.1
p value*	0.220	0.635	0.314 ↑	0.35 ↑	0.401 ↑ ↑	0.266	0.441	0.404	0.005	0.297

Table 1. Baseline characteristics of subjects in test and control groups
Smoking and Alcohol drinking habit Y: yes; N: no; F: former
*: Comparison between groups
†: Ten subjects in test group and 9 subjects in control group
‡: 11 subjects in test group and 8 subjects in control group

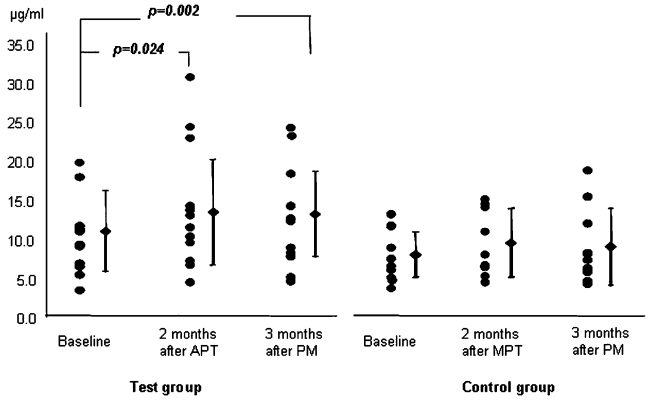

Fig. 2. The distribution of serum adiponectin in the two groups at baseline, 2 months after APT/MPT and 3 months after PM. Dots represent the individual values of the patients. The means and standard deviations in each group are represented by filled diamonds and error bars.

to the concentrations of adiponectin, TNF-α and hs-CRP in control group at 2 months after MPT or at 3 months after PM. Moreover, HbA1c values increased from 7.1% to 7.4% in test group and from 7.5% to 7.8% in control group at 2 months after APT/MPT. The values at 3 months after PM also sustained higher levels compared with baseline. However, there were no significant differences among the HbA1c values at these time points in both groups.

According to the results of the correlation analysis among adiponectin, TNF-α, hs-CRP and the percentage of sites with ⩾4 mm PD after APT/MPT and after PM in both groups, it was shown that adiponectin had not been significantly correlated to any of these markers in both groups though periodontal treatments were given. However, after PM a negative relationship between adiponectin and TNF-α in test group was observed ($r = -0.661$, $p = 0.027$). A positive correlation between hs-CRP and the percentage of sites with ⩾4 mm PD ($r = 0.804$, $p = 0.003$) in test group was also found. In contrast, no correlations of these markers in control group were detected (results not shown).

Discussion

A number of small studies indicated that periodontal treatment has a positive effect on the control of T2DM (Stewart et al. 2001, Kiran et al. 2005, Navarro-Sanchez et al. 2007). Some studies have also observed that APT may have a considerable impact on diabetic control (Grossi et al. 1997, Rodrigues et al. 2003, Promsudthi et al. 2005). Iwamoto et al. (2001, 2003) postulated that APT decreases TNF-α and hs-CRP and enhances subsequent metabolic control of diabetes including improvement of insulin resistance.

Adiponectin has enhanced insulin sensitivity (Yamauchi et al. 2002) and suppressed the production and activity of TNF-α in T2DM patients (Yokota et al. 2000, Nishimura et al. 2003, Wolf 2003, Kadowaki et al. 2006, Whitehead et al. 2006). In addition, adiponectin has

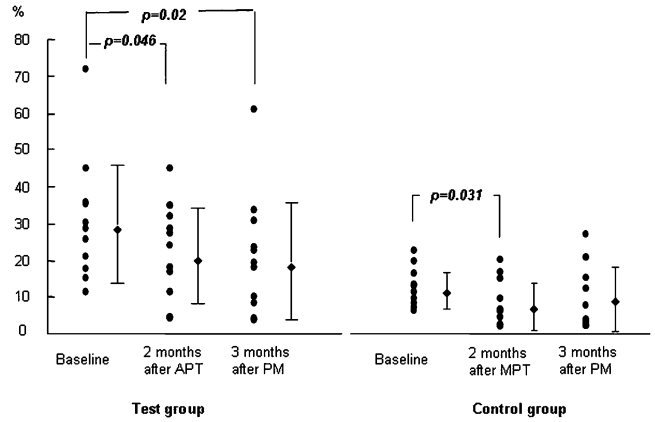

Fig. 3. The distribution of percentage of sites with ⩾4 mm PD at baseline, 2 months after APT/ MPT and 3 months after PM in both groups. Dots represent the individual values of the patients. The means and standard deviations in each group are represented by filled diamonds and error bars.

an anti-inflammatory role (Yokota et al. 2000, Ouchi et al. 2001). Therefore, we postulated that improvement of periodontal status by APT might contribute to increase serum adiponectin in T2DM.

Our results showed that the test group who received APT had a greater increase in serum adiponectin levels and much improved periodontal status compared with the group received periodontal treatment alone. PM followed by APT also contributed to improve serum adiponectin level and periodontal status compared with that at baseline. However, we failed to detect any concomitant effect of APT on serum TNF-α in this study. According to Iwamoto et al. (2003), the reduction in TNF-α was very small while APT improved insulin resistance in T2DM patients. Talbert et al. (2006) has shown that APT increases TNF-α level until after 3 months of therapy in T2DM patients. Bullo et al. (2002, 2003) reported that serum TNF-α does not reflect the TNF-α activity appropriately because TNF-α is a highly labile cytokine, which seems to be used locally, providing autocrine effects (Arner 2003, Wolf 2003). Accordingly, it may be difficult to reflect the local and systemic improvement of APT by the effect of TNF-α alone. Although the differences between serum adiponectin, TNF-α, hs-CRP, HbA1c and the percentages of 4 mm+PD after APT/MPT and PM did not achieve statistical significance, serum adiponectin level in test group improved after APT and PM in this study. Accordingly, it can be concluded that APT may have a positive effect on serum adiponectin concentration in T2DM.

Moreover, APT has not contributed to a reduction of HbA1c values in our study though some studies have indicated that APT may play a role in reducing HbA1c in T2DM patients (Grossi et al. 1997, Iwamoto et al. 2001, 2003). The Japan Diabetes Clinical Data Management Study Group has reported that the mean HbA1c level was around 7.2% for controlled diabetics in the oral hypoglycemic agents group in 2000–2002 (Kobayashi et al. 2006). This finding is in-line with the mean value in our study. However, a few subjects who showed steep fluctuations in HbA1c levels may have influenced our results, ultimately increasing the overall mean HbA1c, which has been further affected by small sample size in our study. Uysal et al. (1997) has also indicated that adiponectin mainly affects insulin receptors which are a part of insulin sensitivity cascade rather than HbA1c level.

Our findings may also postulate that PM followed by APT might be necessary to maintain a good glycemic control and periodontal status in T2DM patients (Ouchi et al. 2003, Pastagia et al. 2006). According to a position paper by the American Academy of Periodontology in (2003), the goals of PM are to prevent or minimize the recurrence and progression of periodontal disease in patients who have been previously treated for gingivitis, periodontitis and peri-implantitis. In longitudinal clinical studies, the reductions in mean PD (Kiran et al. 2005, Cortelli et al. 2006, Bogren et al. 2008) have been observed for at least 3 months in T2DM patients who were provided with APT. Therefore, PM at 3–4 month intervals might improve periodontal status as well as metabolic control in T2DM patients (Renvert & Persson 2004). Our results showed that adiponectin levels of patients in the test group have been significantly increased 9 months after APT compared with baseline level. It might further indicate that PM could preserve the long-term increases of adiponectin by APT.

We have monitored the long-term change of adiponectin induced by APT in this study. However, there are some limitations that may have restricted the scope of the study as well as interpretation of the findings. For instance, one of our inclusion criteria was that there should be no change in diabetic treatment 3 months before and during the study, which in turn may have limited the scope in the long run. Furthermore, considering ethical issues involved, only the patients with relatively good diabetic control were included into the study. Because of limited sample size, the attribution of study population could be disproportionate and the variation of individuals may have also been arisen. These factors may influence the adverse effects of APT on other serum markers that were investigated in this study.

It also remains unclear whether APT and PM uphold beneficial changes of APT on serum adiponectin levels because according to this study design, the subjects in the control group were not considered as untreated while all subjects included in this study received PM. Therefore, further studies where the control group virtually receives neither periodontal treatment nor maintenance would be essential in order to evaluate the exact effect of APT on adiponectin and PM even though the ethical soundness of such study designs might always be controversial.

In conclusion, our results have indicated that APT not only improves periodontal disease but also contributes to increase serum adiponectin concentration as a marker of insulin resistance in T2DM, which is consistent with the theory that periodontal therapy improves metabolic control of patients with T2DM. In addition, PM, followed by APT may contribute to sustain serum adiponectin concentration in the long run.

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Clinical Relevance

Scientific rationale for the study: APT induced periodontal improvement in T2DM patients may be involved in systemic inflammation as well as insulin resistance. Adiponectin relates to reduction of inflammation and insulin resistance.

Principal findings: APT and PM demonstrated improvements in serum adiponectin concentrations that were sustained over 9 months while decreasing the proportion of $\geqslant 4$ mm PD.

Practical implications: APT may improve not only periodontal disease but also insulin resistance by increasing serum adiponectin. PM may also enhance insulin resistance in T2DM patients.