Inflammatory Cytokines, Adiponectin, Insulin Resistance and Metabolic Control after Periodontal Intervention in Patients with Type 2 Diabetes and Chronic Periodontitis

Wei-Lian Sun, Li-Li Chen, Su-Zhan Zhang, Yan-Min Wu, Yue-Zhong Ren and Guang-Ming Qin

Objective To evaluate the effects of periodontal intervention on inflammatory cytokines, adiponectin, insulin resistance (IR), and metabolic control and to investigate the relationship between type 2 diabetes mellitus (T2DM) and moderately poor glycemic control and chronic periodontitis.

Methods and Patients A total of 190 moderately poorly controlled (HbA1c between 7.5% and 9.5%) T2DM patients with periodontitis were randomly divided into two groups according to whether they underwent periodontal intervention: T2DM-NT and T2DM-T group. The levels of serum adiponectin, C-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), lipid profile, glucose, insulin, homeostasis model of assessment - insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-β) were measured at baseline and after 3 months.

Results The levels of clinical periodontal variables, the probing depth, attachment loss, bleeding index, and plaque index were improved significantly in T2DM-T group after 3 months compared to T2DM-NT group (all p<0.01). After 3 months, the serum levels of hsCRP, TNF-α, IL-6, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS) and HOMA-IR index decreased, and adiponectin was significantly increased in T2DM-T group compared to those in the T2DM-NT group (p<0.05 or p<0.01).

Conclusion Periodontal intervention can improve glycemic control, lipid profile and IR, reduce serum inflammatory cytokine levels and increase serum adiponectin levels in moderately poorly controlled T2DM patients.

Key words: Type 2 diabetes mellitus, periodontitis, insulin resistance, adiponectin, inflammatory cytokines

proximately 70% in China.

Recent findings indicate that chronic low-grade inflammation is closely involved not only in the pathogenesis of T2DM and its complications (3), but also in the pathogenesis of periodontal diseases (3-5), whereby cytokines play a central role in the host’s response to the periodontal biofilm. And there is a bidirectional relationship between the mechanisms of T2DM and periodontitis (6). DM adversely affects periodontal condition and periodontitis adversely influences glycemic control, increasing the risk of complications in the diabetic patients (7), while the acute mechanism is still unclear. Genco et al (5) found that subjects with DM and insulin resistance (IR) had more severe periodontitis than those without. IR plays a central role in the development of T2DM (8). Adiponectin, the major adipocyte secretory protein, has been thought to be associated with IR (9) and plays an important negative regulatory role in some physiological and pathological processes (10).

Evidence suggests that periodontal therapy can decrease the intraoral bacterial bioburden, periodontal inflammation, and inflammatory cytokines (3, 11), and it can improve glycemic control (12). Our previous study also showed the beneficial effect of periodontal therapy on diabetes with acceptable glycemic control (HbA1c between 6.5% and 7.5%) (13), in contrast to the studies of Jones et al (14) and Lalla et al (15).

Little is known about the mechanisms through which periodontal treatment may influence the diabetic state, and the impact of initial periodontal treatment on inflammatory cytokines, adiponectin, IR, and metabolic control in T2DM patients, especially in those with moderately poor glycemic control (HbA1c between 7.5% and 9.5%). Thus, investigations on periodontal intervention are necessary to better understand the relationships linking these two conditions. The present study aimed to evaluate the effects of initial periodontal intervention on inflammatory cytokines, adiponectin, IR, and metabolic control to investigate the relationship between T2DM and periodontitis.

**Subjects and Methods**

**Subjects**

A total of 190 unrelated T2DM patients with periodontitis treated at our hospital were enrolled from August 2008 to November 2010. They were diagnosed according to the WHO diagnostic criteria (1999). All patients were encouraged to maintain their regular physical activity and lifestyle throughout the study. The inclusion criteria was as follows: 1) patients diagnosed with T2DM over one year; 2) patients with moderately poor glycemic control (HbA1c between 7.5% and 9.5%); 3) not older than 70 years; body mass index (BMI) between 19 kg/m² and 26 kg/m² in women, BMI between 20 kg/m² and 27 kg/m² in men; 4) no medication changes during the 3 months of study; 5) not smoking; 6) without severe complications, such as diabetic nephropathy, stroke, angina, myocardial infarction and so on. The diagnosis of periodontitis met the following conditions: 1) with over 20 teeth, probing depth (PD) over 5 mm, more than 30% teeth with attachment loss (AL) over 4 mm, or over 60% teeth with PD >4 mm and AL >3 mm; 2) without periodontal treatment in the previous 6 months; 3) without antibiotics or non-steroidal anti-inflammatory drugs administered in the last 3 months; 4) Without serious systemic diseases or complications. Patients with systemic inflammatory diseases (rheumatoid arthritis, etc.), blood disease, liver damage, kidney disease or trauma were excluded.

All of the T2DM patients were randomly divided into two groups according to whether they underwent periodontal intervention: T2DM-NT group and T2DM-T group. A total of 33 patients did not finish the study. The reasons for dropping out included withdrawal due to personal reasons (such as sickness, no available time) (12 patients), later follow-up visit (21 patients, over 3 months). The data of these patients have been excluded from the data at the baseline (Table 1, 2).

T2DM-NT group consisted of 75 patients, 32 males and 43 females, aged from 36 to 70 years with a mean age of 54.23 ± 10.85 years and a mean BMI of 23.89 ± 2.73 kg/m². T2DM-T group consisted of 82 patients, 35 males and 47 females, aged from 37 to 70 years with a mean age of 55.13 ± 11.16 years and a mean BMI of 23.71±2.84 kg/ m². There were no significant differences in sex distribution, age, and BMI among the groups (all p>0.05).

Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of the Second Hospital of Zhejiang University College of Medicine.

**Clinical periodontal examination**

PD and AL of all the remaining teeth were measured. Six sites of PD and AL, including the middle of the near, the central and the far in both buccal and palatal sides, were recorded and the average was calculated. Sulcus bleeding index (BI) and plaque index (PLI) were also measured.

**Periodontal intervention**

Periodontal intervention included oral hygiene, full-mouth scaling (supragingival and subgingival scaling), root planning, periodontal flap surgery when indicated, and extraction of hopeless teeth, restore of balanced occlusion. Antibiotics (Tinidazole 1.0 g, bid, po. and ampicillin 0.25 g, qid, po.) were prescribed for 3 days before and after periodontal intervention. All periodontal interventions were performed by one periodontist.

**Biological measurement**

Blood samples were taken after overnight fasting and the levels of the following compounds were measured at baseline and after 3 months with or without periodontal intervention.

Serum adiponectin (Linco Research, St. Louis, MO, USA), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6)
Table 1. Periodontal Status in T2DM Patients with and without Periodontal Intervention after Three Months

<table>
<thead>
<tr>
<th></th>
<th>without intervention</th>
<th>with intervention</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>After 3 Mos</td>
</tr>
<tr>
<td>Number</td>
<td>75</td>
<td>75</td>
</tr>
<tr>
<td>PD (mm)</td>
<td>4.49±0.85</td>
<td>4.28±0.81</td>
</tr>
<tr>
<td>AL (mm)</td>
<td>4.88±1.39</td>
<td>4.73±1.29</td>
</tr>
<tr>
<td>BI</td>
<td>2.97±0.66</td>
<td>2.86±0.64</td>
</tr>
<tr>
<td>PLI</td>
<td>2.47±0.70</td>
<td>2.18±0.69</td>
</tr>
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</table>

Results are given as mean±SD.

Compared with those without periodontal intervention after three months, ##: p<0.01.

Compared with Δ of those without periodontal intervention after three months, **: p<0.01.

T2DM, type 2 diabetes mellitus; PD, probing depth; AL, attachment loss; BI, bleeding index; PLI, plaque index.

Statistical analysis

Statistical analyses were performed using SPSS software (16.0 version). Quantitative data were presented as mean ± S.D. The statistical significance between means was estimated by one-way ANOVA followed by LSD multiple comparisons or Student’s t test (Independent Samples) when appropriate. The data which did not present Gaussian distribution were log-transformed and analyzed: HOMA-IR and HOMA-β differences were considered statistically significant at p<0.05.

Results

Table 1 shows the main periodontal characteristics of the study sample regarding data collected during the clinical oral examination in T2DM patients at baseline and after 3 months. The levels of clinical periodontal variables including PD, AL, BI, and PLI, were improved significantly in T2DM-T group after 3 months than those in the T2DM-NT group (all p<0.01). ΔPD, ΔAL, ΔBI and ΔPLI were statistically significant in the T2DM-T group after 3 months compared to those in the T2DM-NT group (all p<0.01).

Diabetes mellitus remains a chronic metabolic disorder that is often associated with an unacceptably high disease burden especially in developing countries (17), and cardiovascular (CVS) complications of DM are highly contributory to this scenario. In recent years, inflammation has been regarded to be involved in the pathogenesis of IR and T2DM, which are regarded as key processes in the mechanism of T2DM (8). The relation between periodontal health and diabetes has been described as bidirectional (6). Evidence has consistently indicated that diabetes is a risk factor for increased severity of gingivitis and periodontitis (4). Poor glycemic control is involved in the development of periodontitis (18), and the risk of periodontitis is reduced by effective control of hyperglycemia (19).

In this study, we noted that DM with moderately poor glycemic control had moderate to severe periodontitis, which indicates that poor glycemic control is the most significant risk factor associated with the severity of periodontitis. Our study provides further information on T2DM patients with periodontitis in the Chinese population, and pro-
Table 2. Comparisons of the Biological Parameters and Inflammatory Factors in T2DM Patients with and without Intervention after Three Months

<table>
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<tr>
<td></td>
<td>Baseline</td>
<td>After 3 Mos</td>
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</tr>
<tr>
<td>Number</td>
<td>75</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>9.75 ± 1.72</td>
<td>9.31 ± 1.69</td>
<td>-0.44 ±0.24</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.70 ±0.65</td>
<td>8.56 ±0.69</td>
<td>-0.14 ±0.12</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>2.10 ±0.68</td>
<td>2.08 ±0.66</td>
<td>-0.02 ±0.02</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.15 ±0.28</td>
<td>1.16 ±0.30</td>
<td>-0.01 ±0.03</td>
</tr>
<tr>
<td>LDL-C (mmol/L)</td>
<td>3.37 ±0.74</td>
<td>3.31 ±0.75</td>
<td>-0.06±0.10</td>
</tr>
<tr>
<td>FINS (mU/L)</td>
<td>11.56±3.21</td>
<td>11.32±3.19</td>
<td>-0.24±0.46</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>5.01±1.46</td>
<td>4.68±1.39</td>
<td>-0.32±0.29</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>36.99±8.34</td>
<td>37.67±9.89</td>
<td>0.68±0.87</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>5.81±1.23</td>
<td>5.51±1.29</td>
<td>-0.30±0.31</td>
</tr>
<tr>
<td>TNF-α (ng/ L)</td>
<td>11.54±2.27</td>
<td>11.37±2.35</td>
<td>-0.17±0.32</td>
</tr>
<tr>
<td>IL-6 (ng/L)</td>
<td>10.73±2.52</td>
<td>10.42±2.43</td>
<td>-0.31±0.33</td>
</tr>
<tr>
<td>APN (mg/L)</td>
<td>7.99±2.10</td>
<td>8.35±2.13</td>
<td>0.36±0.43</td>
</tr>
</tbody>
</table>

Results are given as mean±SD. Compared with those without periodontal intervention after three months, #: p<0.05, ##: p<0.01. Compared with Δ of those without periodontal intervention after three months, **: p<0.01.

T2DM, type 2 diabetes mellitus; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FINS, fasting insulin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C reactive protein; TNF-α, Tumor necrosis factor; IL-6, interleukin-6; APN, adiponectin.

provides data on the HOMA index, a biological marker of IR.

Previous studies led to conflicting results as to whether or not periodontal therapy impacts glycemic control with T2DM. In the present study, we noted that PD, AL, BI and PLI were significantly decreased in the T2DM-T group after 3 months as well as the HbA1c, FINS and HOMA-IR levels, and ΔHOMA-β increased significantly. These results confirmed our hypothesis that periodontal treatment not only reduces clinically evident inflammation, but also improves the glycomic control and reduces IR and improves β cell function in T2DM patients. These findings indicate that inflammation is involved in the pathogenesis of IR and T2DM, which is regarded as key processes in the mechanism of T2DM (8). However, Jones et al indicated that periodontal therapy has no statistically significant effect on glycemic control (14). This could be attributed to considerable differences in methodology, sample sizes and composition of the groups included in the studies.

The mechanisms through which periodontal diseases may influence the diabetic state are still unclear. In untreated severe periodontal disease, the cumulative surface area of ulcerated pocket epithelium has been estimated to range from 8 to 20 cm², which is approximately the size of the palm of an adult hand (20). Increasing evidence suggests that severe chronic periodontitis represents a sub-clinical septicemic state (21). It can produce some inflammatory cytokines (e.g. CRP, TNF-α and IL-6) in the local tissue, as well as elevating their circulating levels (13, 22, 23). CRP is an important mediator of inflammation, mainly synthesized in the liver. TNF-α is another important inflammatory cytokine, closely linked to IR (23), which plays a role in the regulation of CRP expression. Several studies showed that circulating CRP and TNF-α levels are increased in T2DM patients with periodontitis (13, 22, 23). Adiponectin is the only adipocytokine identified to date, secreted specifically by mature adipocytes, which plays an important negative regulatory role in some physiological and pathological processes (10), including multiple protective roles such as antidiabetic, anti-atherosclerotic, and anti-inflammatory factors (24). It regulates glucose and lipid metabolism, improves insulin sensitivity, reduces hepatic glucose production, and has anti-inflammatory and protective effects on vascular lesions. Previous studies showed that hypoadiponectinemia is correlated with increased hyperinsulinemia and IR during the development of IR and T2DM (25).

In the present study, HbA1c and HOMA-IR decreased significantly, as well as the levels of hsCRP, TNF-α and IL-6, while adiponectin increased significantly compared to those without periodontal intervention three months after periodontal intervention. Therefore, periodontal intervention is helpful for glucose control and insulin sensitivity improvement, which may be associated with decreased serum...
inflammatory cytokines and increased serum adiponectin levels (22).

The acute mechanism of these inflammatory cytokines still remains unclear. It may be associated with improved insulin sensitivity, glucose and lipid metabolism by reduction of inflammatory cytokines. Nishimura et al (22) found that chronic periodontal inflammation can lead to increased serum levels of TNF-α, thus inducing the phosphorylation of serine residues in the insulin receptor substrate-1, prompting the target cells to produce IR, also acting on the liver to increase CRP synthesis. Several studies suggested that TNF-α and other inflammatory mediators may activate the intracellular pathways, such as the I-kappa-B (IκB), I-kappa-B kinase-β (IKKβ), nuclear factor-kappa B (NF-κB) and the protein c-Jun N-terminal kinase (JNK) axes, amplify and aggravate low-grade inflammation, and these processes may become self-perpetuating through a positive feedback loop created by the proinflammatory cytokines, and lead to IR and diabetes (26).

The risk of developing coronary artery disease (CAD) in diabetic patients is two to four times greater than that of non-diabetics, and diabetics with no history of previous myocardial infarction (MI) have the same risk of future cardiovascular events as non-diabetics who have suffered a previous heart attack (27). Recent studies indicated that periodontitis may be a risk factor for worsening glycemic control, impairing endothelial function among patients with diabetes, and also may increase the risk of cardiovascular events, such as myocardial infarction and stroke. hsCRP and HDL are two risk markers for cardiovascular disease (28, 29). And an epidemiological extrapolation from the UK Prospective Diabetes Study (UKPDS) predicts that for every 1% reduction in HbA1c there would be an associated 21% reduction in risk for any diabetes-related endpoints, including both microvascular (37% reduced risk of microvascular complications) and macrovascular (14% reduced risk of myocardial infarction) complications (30). In the present study, after periodontal intervention, we also noted that hsCRP, TNF-α, as well as HbA1c and HOMA-IR decreased, and ΔHDL-C was significantly changed, which indicated that treatment of periodontitis may improve vascular health, and reduce the risk of future cardiovascular events (30).

This study has several limitations. The study was not blinded and it was performed at a single facility. Elderly persons, obese subjects, and those with several diabetic complications were excluded. So it remains uncertain whether the results of this study can generalized to other diabetic populations.

In conclusion, our data showed that periodontal intervention is helpful for glucose control, which may be associated with reduced inflammatory cytokine levels, increased adiponectin, and help to restore insulin sensitivity, thereby improving glycemic control. And we also noted hsCRP and HbA1c were decreased and adiponectin was increased after periodontal intervention, which suggested that the periodontal intervention may also possibly reduce their risk of cardiovascular diseases.

In the management of diabetes, maintaining good glycemic and lipid control are therapeutic objectives to reduce cardiovascular risk. Recognition of the bilateral relationships between periodontitis and T2DM will challenge endocrinologists and dentists to work together closely in the future when managing patients with diabetes and periodontal disease. The results of this study will help to provide evidence-based recommendations for clinicians and facilitate drafting a framework for designing local and national health policies.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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