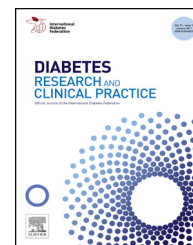


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# Improvement of glycated hemoglobin in Japanese subjects with type 2 diabetes by resolution of periodontal inflammation using adjunct topical antibiotics: Results from the Hiroshima Study<sup>☆</sup>

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## ABSTRACT

**Aims:** Periodontal treatment reduces glycated hemoglobin (HbA1) in subjects with type 2 diabetes, although effective strategy for different severities of periodontitis remains unclear. We hypothesized that resolution of periodontitis-induced inflammation by the therapy combined with antibiotics may have beneficial effects on the glycemic control of diabetes.

**Methods:** A total of 523 subjects with type 2 diabetes were screened for periodontal disease. Of these, 160 subjects who visited dentists were divided into two groups according to high-sensitivity c-reactive protein (hsCRP) level: >500 ng/ml and <500 ng/ml. The group with hsCRP over 500 ng/ml was further sub-divided into two groups according to treatment strategy: topical application of antibiotics combined with conventional mechanical debridement (group A), and debridement alone (B). Subjects with hsCRP below 500 ng/ml were sub-divided similarly (C: combination therapy; D: debridement alone). hsCRP was measured after 1 month and changes of HbA1c after 3 months. These parameters were also measured in control subjects (N = 118) who did not visit dentists (E: initial hsCRP > 500 ng/ml; F: hsCRP < 500 ng/ml).

**Results:** A multiple comparison by ANOVA revealed that only group A showed a significant reduction in HbA1c over time (P < 0.001). Multivariable analyses revealed elevated hsCRP and the combination treatment with antibiotics were two independent variables influencing the decrease of HbA1c over the study (P < 0.01 and P < 0.001, respectively).

**Conclusions:** In subjects with type 2 diabetes and periodontitis-induced mild inflammation (hsCRP > 500 ng/ml), treatment to reduce hsCRP using antibiotics is recommended.

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<sup>☆</sup> Clinical trial registration: The study protocol was registered in UMIN clinical trial registry (clinical trial registration number: UMIN000006356).

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<sup>1</sup> Members of the Hiroshima Study Group are listed in the appendix section. 0168-8227/\$ – see front matter © 2013 Elsevier Ireland Ltd. All rights reserved. <http://dx.doi.org/10.1016/j.diabres.2013.01.028>

## 1. Introduction

Periodontal disease is one complication of diabetes mellitus. Recent epidemiological studies suggest that periodontal disease itself may cause a deterioration of glycemic control. For example, the National Health and Nutrition Examination Survey (NHANES) I study indicated that severe periodontal disease at baseline was associated with development of diabetes over 20 years of follow-up [1]. A separate study indicated that severe periodontal disease might also be associated with deterioration in hemoglobin A1c (HbA1c) levels even among non-diabetic subjects [2]. In this study, the subjects with levels of circulating c-reactive protein (CRP) over 1000 ng/ml showed accelerated deterioration of HbA1c over a 5-year follow-up period, suggesting that periodontitis-induced low-grade inflammation was associated with the deterioration of glycemic control. Given these findings, one may speculate that treatment of periodontal disease has beneficial effects on the metabolic control of diabetes. A recent meta-analysis also indicated that HbA1c improved by an average of 0.4% with periodontal treatment [3]. This estimate was based on comprehensive analyses of several studies comprising 371 cases; however, the studies included in this meta-analysis may have differed in terms of subjects' ethnicity, methods of diabetes management, and design of intervention [3].

Our previous pilot study on the metabolic control of diabetes suggested that periodontal treatment may improve HbA1c by amelioration of insulin resistance due to remission of periodontitis-induced systemic inflammation [4]. Studies suggest that some, but not all, periodontal diseases evoke systemic low-grade inflammation, which may aggravate insulin sensitivity.

It is still unclear whether the beneficial effects of periodontal treatment vary with the degree of periodontitis, and which periodontal treatments are most effective for improving metabolic control of diabetes. The Hiroshima Study was undertaken to answer these questions in Japanese subjects with type 2 diabetes and periodontal disease.

## 2. Subjects and methods

### 2.1. Study population

A total of 523 Japanese subjects with type 2 diabetes were enrolled into the study. All patients routinely attended a diabetes clinic in the Hiroshima Prefecture with a Japan Diabetes Society certified diabetes specialist. The study was performed from November 2008 to July 2012. Prior to screening for periodontal disease, the following subjects were excluded: those with type 1 diabetes, subjects who were pregnant, subjects who had received periodontal treatment or antibiotics in the past 3 months, subjects receiving anti-inflammatory medication such as for rheumatoid arthritis, and subjects with chronic fatigue disease, acute illness, or depression. Subjects were initially screened by dentists from Hiroshima Prefectural Dental Association. Initial screening included (1) counting the number of remaining teeth, (2) checking for gingival inflammatory signs such as redness and

swelling, and (3) checking for accumulation of dental plaque and calculus. Subjects with fewer than ten remaining teeth or with edentulous were excluded. Most subjects excluded at this screening stage had an insufficient number of remaining teeth. A total of 434 subjects were selected and recommended to visit a dentist for detailed periodontal care. Among them, 236 subjects visited dentists, and of these, 160 subjects received periodontal treatment. The other 76 subjects were excluded from the study because of concomitant infection of another organ at the time of the dental visit or insufficient number of remaining teeth. Several patients did not agree to participate in the study after detailed explanation of the protocol, which required at least four additional visits. The remaining 198 subjects did not visit dental offices despite the dentist's recommendation; however, of these, 118 subjects agreed to participate in the study as a control group (non-treatment group). High sensitivity CRP (hsCRP) and HbA1c values were recorded in all 160 subjects who visited dentists and received periodontal treatment and in 118 subjects who did not visit dentists. HbA1c was measured by latex coagulating method, while hsCRP was measured by latex nephelometry method. Both parameters were measured by commercial medical laboratory (SRL Inc., Tokyo, Japan).

### 2.2. Study protocol

For all 160 patients who visited dental clinics, panoramic radiographs were taken to calculate bone resorption score. We first divided the 160 subjects into two groups based on their hsCRP value;  $>500$  ng/ml and  $<500$  ng/ml. This cut-off point was based on results from the recently reported Hisayama study in Japanese subjects, which showed that half the study population had hsCRP  $> 500$  ng/ml and an hsCRP above this level was associated with an approximately two-fold greater risk of both cardiovascular events and cardiovascular death [5]. In addition, the Japanese Society of Periodontology recently classified periodontal disease severity based on inflammatory markers and periodontal bone resorption ratio as measured by panoramic radiograph. According to this classification, subjects with hsCRP over 500 ng/ml and a bone score over 25% are considered to have mid- to severe-periodontitis at both inflammatory and clinical levels. Therefore, we defined our subjects with hsCRP over 500 ng/ml as having low-grade systemic inflammation. We treated approximately half of the subjects in both the high and low hsCRP groups with anti-microbial treatment combined with conventional mechanical debridement such as scaling and root planning. In this study, we chose to treat with topical application of antibiotics to selectively investigate the effectiveness of antibiotic treatment for periodontal infection rather than other infections. In these subjects, tetracycline-HCl ointment (Perioline 1.5 g, Sunstar, Osaka, Japan) was applied into every periodontal pocket and gingival sulcus once a week for 4 weeks. After remission of gingival inflammation by this chemotherapy, we carefully removed tooth debris to prevent bleeding by mechanical debridement to avoid further bacteremia. The remaining subjects underwent conventional mechanical debridement. This treatment composed of scaling and root planning including ultrasonic scaling. This approach was repeated four times so that the number of visits was the

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