2014 Periodontal Treatment Guidelines for Patients with Diabetes (Revised Version 2)

CQ Number	CQ
1	CQ1 Is periodontal treatment effective for improvement of HbA1c?
2	CQ2 Is periodontal disease improved by glycemic control?
3	CQ3 Is education to encourage patients with diabetes to establish a habit of mouth cleaning effective for maintenance of favorable glycemic control?
4	CQ4 As periodontal treatment for patients with diabetes, is concomitant use of local or oral antimicrobial therapy more effective, compared to a single procedure of scaling root planing (SRP)?
5	CQ5 Is treatment for bacteremia necessary in basic periodontal treatment for patients with diabetes?
6	CQ6 What level of glycemic control should be achieved in invasive procedures such as periodontal surgery in patients with diabetes?
7	CQ7 Should warfarin be suspended when patients with diabetes undergo dental extraction, basic periodontal treatment, or periodontal surgery?
8	CQ8 Should more thorough administration of antimicrobial drugs be used in surgery for patients with diabetes?
9	CQ9 Can patients with diabetes obtain therapeutic effects of periodontal guided tissue regeneration equivalent to those in non-diabetes patients?
10	CQ10 Can patients with diabetes obtain therapeutic effects of implant treatment equivalent to those in non-diabetes patients?
11	CQ11 Does periodontal disease easily redevelop in the period of supportive periodontal therapy (SPT) in patients with diabetes?
12	CQ12 Should the interval of SPT be shorter for patients with diabetes, compared to other patients with periodontal disease?
13	CQ13 What level of glycemic control should be provided to patients with diabetes in the SPT period?

	CQ/Contents	CQ1 Is periodontal treatment effective for improvement of HbA1c?
1	Recommendation/response	A systematic review and meta-analysis of a randomized comparative study suggested significant improvement of HbA1c by 0.36% after periodontal treatment, but some reports are negative. However, there is counterevidence for the negative reports, and several meta-analyses support the effects of periodontal treatment for improvement of glycemic control. Therefore, periodontal treatment is likely to be effective for patients with diabetes, and is recommended for these patients.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 1[note]
Explanation		Note) Randomized control trials (RCTs) other than high-quality randomized comparative studies, and related meta-analyses or systematic reviews

Background/objectives:
The relationship between periodontal disease and diabetes has long been discussed in the literature. A recent Japanese large-scale epidemiological study confirmed an interaction of these diseases. The effects of periodontal treatment for patients with diabetes were first reported by Grossi et al. in 1997. However, the results of many subsequent studies have been inconsistent. A meta-analysis from 5 years ago showed no significant effects. Since many new studies have been performed since this analysis, we performed a new search.

Explanation:
A meta-analysis by Simpson et al. in 2010 showed that scaling root planing (SRP) and oral hygiene instruction (with or without antimicrobial therapy) significantly decreased HbA1c by 0.4% ($p = 0.04$) in 3-4 months after treatment. A meta-analysis by Teeuw et al. in the same year showed similar results. A meta-analysis in 2013 suggested improvement of HbA1c by 0.36% ($P<0.0001$).

Simpson et al. reviewed 7 studies and included 3 in the meta-analysis. Five studies were examined in Teeuw et al., but 3 of these were the studies included in Simpson et al. In the 2013 meta-analysis, 9 studies were selected from those published since October 2009, using the same method as that of Simpson et al. Among these 9 studies, 3 included data for more than 100 subjects, and the periodontal disease conditions at the start of the studies varied from gingivitis to severe periodontitis. Treatment of periodontal disease for the test group included oral hygiene instruction and subgingival SRP, as well as general (4 subjects) and local (1 subject) administration of antimicrobial drugs as adjunctive treatment. In a randomized clinical trial in 475 subjects performed in 2013, Engebretson et |

al. found that clinical conditions of periodontal disease were significantly improved with no improvement of HbA1c in patients treated with oral hygiene instruction, SRP, and gargling of chlorhexidine, compared to untreated controls. In a clinical study in Japan in 278 subjects, there was significant improvement of HbA1c 3 months after SRP and local administration of minocycline in patients with a hs-CRP ≥500 ng/mL (type 2 diabetes + moderate to severe periodontitis). Differences between these studies included race, age, and body mass index (BMI). The age of the Japanese subjects was higher (57 vs. 66 years old), and BMI was significantly higher in the US study (34-35 vs. 22-25 kg/m^2). hs-CRP increased by severe periodontitis might have been compensated for by inflammation caused by obesity in subjects with high BMI in the US study, and thus inflammation caused by obesity might have affected the results. A counterargument to Engebretson et al. suggested that the disputed validity may be due to ① an average HbA1c level of 7.8% at baseline close to the target for improvement, ② improvement of periodontal disease after treatment that was less than standard values in other reports, and ③ improvement of inflammation by periodontal treatment masked by severe obesity. In addition, the average probing pocket depth (PPD) in the treatment group was 3.3 mm, which is close to the normal range, which raises doubts about the severity of periodontal disease. In an interventional study in China in subjects with BMI relatively close to that of Japanese patients with diabetes, Chen et al. found that HbA1c tended to improve in follow-up observation for 6 months after SRP under local anesthesia, but without a significant effect. In contrast, in comprehensive periodontal treatment, including pre- and postoperative use of antimicrobial drugs, SRP, extraction of unsustainable teeth, and flap surgery, Sun et al. found a significant improvement of HbA1c (0.5%) 3 months after treatment. The difference between these studies include the severity of periodontal disease, HbA1c, and hs-CRP level at baseline. In Chen et al. vs. Sun et al., average PPD, attachment level, HbA1c, and hs-CRP were 2.5 vs. 4.5 mm, 3.3 vs. 4.9 mm, 7.3% vs. 8.7%, and 3 vs. 5.8 mg/L, respectively. In addition, Sun et al. performed comprehensive periodontal treatment, including flap surgery and antimicrobial drugs, and achieved improvement of periodontal disease and a decrease of hs-CRP, while Chen et al. used only SRP, which resulted in a lower level of improvement of periodontal disease. This suggests that improvement of HbA1c might be affected by the severity of periodontal disease at baseline, diabetes status, level of systemic inflammation and improvement after treatment, and differences in periodontal treatment methods and attendant therapeutic effects.

As mentioned above, improvement of HbA1c was found in a meta-analysis, but there were several problems, including the small number of reports used in the analysis, insufficient number of cases, difficulty with comparison due to various conditions of periodontal disease and diabetes treatment in each study, and unclear improvement of periodontal disease. In addition, effects on inflammation at sites other than the oral cavity should be taken into consideration when antimicrobial drugs are concomitantly used. However, based on the systematic review and interventional studies in Japanese and Chinese subjects, there are patients in whom diabetes may be improved by periodontal treatment. In the future, it will be important to examine which periodontal treatment is effective for what type of patient with diabetes more precisely by performing interventional

studies with division of subjects based on status of diabetes, including complications, systemic inflammation, severity of periodontal disease at baseline, and periodontal treatment methods. In particular, it will be desirable to perform interventional studies with a uniform protocol.

CQ/Contents	CQ2 Is periodontal disease improved by glycemic control?

2	Recommendation/response	Since patients with uncontrolled diabetes have high risks of increased severity of periodontal disease and loss of teeth, glycemic control is important. It is ethically difficult to perform a randomized comparative study with a control group with no glycemic control to examine the effects of glycemic control on periodontal disease. In addition, no randomized comparative study has examined these effects in intensified and normal treatment. In a before-and-after controlled trial, gum inflammation improved with improved glycemic control in diabetes treatment, but with no improvement in periodontal pockets and attachment level. More studies of periodontal tissues after diabetes treatment are required. However, the effects of this treatment on these tissues are limited, and improvement of periodontal disease with diabetes treatment is unlikely without periodontal treatment for dental plaque bacteria, the cause of the disease. Since poorly controlled diabetes may be a risk factor for periodontal disease, tight control of diabetes is needed for successful periodontal treatment.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 3[note]
Explanation	Note) Non-randomized comparative study, controlled before-and-after trial, retrospective cohort study, case control study, related meta-analysis or systematic review, and a sub-analysis of a predetermined RCT Background/objectives: Periodontal disease and diabetes are thought to affect each other, and the prevalence and severity of periodontal disease are higher in patients with diabetes, compared to healthy persons. However, the effects of glycemic control on periodontal disease have only been examined in a few studies. Explanation: In a cross-sectional comparative study in patients with diabetes with favorable and poor glycemic control, the severity of periodontal disease was significantly higher in uncontrolled patients. In a longitudinal study of the effects of glycemic control level on progress of periodontal disease in patients with type 1 and 2 diabetes, periodontal disease was significantly aggravated and the risk of tooth loss was higher in patients with poorly controlled type 1 and 2 diabetes, compared to healthy persons. One of the few reports on the effects of diabetes treatment on periodontal disease suggested that gum inflammation is improved		

	by improved glycemic control in diabetes treatment, but there was no significant improvement in periodontal pockets and attachment level.

CQ/Contents	CQ3 Is education to encourage patients with diabetes to establish a habit of mouth cleaning effective for maintenance of favorable glycemic control?

3	Recommendation/response	A favorable mouth cleaning habit may increase self-efficacy of patients with diabetes and prevent development or aggravation of diabetes.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: $4^{note)}$

| Explanation | Note) Cross-sectional study and case accumulation

Background/objectives:
Risk factors for periodontal disease, such as diabetes, and decreased supportive periodontal therapy (SPT) may promote tooth loss, and tighter oral care with professional mechanical tooth cleaning (PMTC) and mouth cleaning should be performed for patients with poor glycemic control in whom periodontal treatment is insufficient. SPT may also improve awareness of patients for oral care (mainly tooth brushing). Other common risk factors for periodontal disease and metabolic syndrome include nutritional balance, insufficient exercise, stress, smoking, alcohol, and insufficient mouth cleaning. Oral cavity management of patients with diabetes is also essential for diabetes management. However, the role of daily mouth cleaning in glycemic control in patients with diabetes has not been clarified. For prevention of development and aggravation of diabetes, interventional studies are required to evaluate oral health multidirectionally in management of diabetes and its complications.

Explanation:
Development and aggravation of periodontal disease and diabetes are related to insufficient mouth cleaning and lifestyle habits (diet, exercise, sleep, stress, smoking, and alcohol). In this CQ, we conducted literature searches on the relationship between mouth cleaning habit (mainly frequency of tooth brushing) and development/aggravation of diabetes; effects of risk markers of metabolic syndrome, diabetes, and its complications; and methods to improve awareness of patients. The incidence and prevalence of metabolic syndrome, level of neutral fat, and hs-CRP level were all found to be significantly higher in subjects who performed tooth brushing once daily or less, compared to those who brushed twice daily or more, suggesting that increased tooth brushing frequency might contribute to prevention of metabolic syndrome.
A study of the self-efficacy of tooth brushing in management of diabetes showed that patients with higher self-efficacy understood their condition of glycemic control, and were healthier and less obese. Close correlations were found between self-efficacy and plaque index, HbA1c level, and tooth brushing habit. Furthermore, cognition of self-efficacy was suggested as a common behavioral factor in oral health action and self-management of diabetes. Based on this, it was suggested that a focus should be placed on diabetes-related behavioral factors (diet, exercise, and blood glucose monitoring) and on oral health factors |

for systemic health promotion in patients with type 2 diabetes. The risk of cardiovascular events was increased (hazard ratio: 1.7) and hs-CRP and fibrinogen levels were higher in subjects with low daily frequency or no habit of tooth brushing. A significant correlation was also found between self-reported mouth cleaning (brushing, flossing, professional care, and condition of the oral cavity) and risk factors for cardiovascular disease (total cholesterol and blood pressure) and systemic inflammation markers (adiponectin, hs-CRP, fibrinogen, and sICAM-1). This suggests that regular tooth brushing is likely to be effective for maintenance of favorable glycemic control and prevention of complications of diabetes, in addition to improvement of high blood pressure, discontinuation of smoking, and decrease of body weight, and that regular mouth cleaning is an essential factor in systemic health management.

Based on these findings, a mouth cleaning habit (tooth brushing) may increase self-efficacy of patients with metabolic syndrome, diabetes, or its complications, and be effective for prevention of development and aggravation of diabetes. Longitudinal interventional studies are required to clarify the causal correlation and medical economic effects.

	CQ/Contents	CQ4 As periodontal treatment for patients with diabetes, is concomitant use of local or oral antimicrobial therapy more effective, compared to a single procedure of scaling root planing (SRP)?
4	Recommendation/response	Concomitant antimicrobial therapy should be considered in basic periodontal treatment for patients with diabetes who develop periodontitis. Such therapy is particularly recommended in cases with diffuse chronic periodontitis that develops with diabetes, severe diabetes-related periodontitis, or severe periodontitis that is difficult to reach using SRP.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 1[note]
Explanation		Note) RCT other than high-quality randomized comparative study, and related meta-analysis or systematic review

Background/objectives:
In summarizing reports on antimicrobial therapy for patients with periodontal disease, a consensus emerged that a supplemental effect of concomitant antimicrobial therapy was unlikely in systematically healthy patients with chronic periodontitis who had a favorable response to normal mechanical plaque control. In contrast, concomitant antimicrobial therapy is thought to be effective for patients with refractory periodontitis or diffuse severe periodontitis who have a poor response to normal treatment. Furthermore, for compromised patients with periodontitis with decreased host biophylactic function due to diabetes with poor glycemic control, and those with periodontitis who have vascular endothelial dysfunction due to arteriosclerotic disease, concomitant antimicrobial therapy is recommended to increase the response to periodontal treatment and decrease adverse effects on the whole body and other organs. Therefore, we examined the effects of concomitant antimicrobial therapy in periodontal treatment for patients with diabetes from a standpoint of improvement of clinical parameters.

Explanation:
We conducted literature searches on improvement of clinical parameters of periodontal tissues (probing pocket depth [PPD], attachment level [clinical attachment loss, CAL], and bleeding on probing [BOP]) due to antimicrobial therapy (local and systemic) concomitantly performed with basic periodontal treatment for patients with diabetes. In two studies of concomitant use of SRP and an oral antimicrobial drug, doxycycline (100 mg/day for 14 days) in patients with type 2 diabetes, there was no significant difference in clinical parameters in evaluation for 3 to 6 months. In a study of concomitant doxycycline (100 mg/day for 15 days) in patients with type 1 diabetes, deep PPD (≥6 mm) and BOP were significantly improved after 3 months, compared to patients treated with SRP alone. In long-term administration of low-dose doxycycline (40 mg/day for 3 |

months) to inhibit collagenase activity, in which antimicrobial effects were expected, a significant improvement of clinical parameters was found in a period of 3-6 months, compared to SRP alone. However, oral administration of amoxicillin concomitantly with one-stage full-mouth SRP (FMSRP), in which SRP is performed for the full mouth within 24 h in patients with type 2 diabetes, did not significantly improve clinical parameters in 3 months, compared to FMSRP alone. Similar improvement of periodontal local inflammation (BOP) was found 9 months after basic periodontal treatment in patients with metabolic syndrome concomitant with SRP and a combination of metronidazole and amoxicillin compared to supragingival scaling alone. In contrast, SRP with an oral combination of metronidazole and amoxicillin in patients who developed diffuse chronic periodontitis with type 2 diabetes showed a significant improvement of clinical parameters, compared to SRP alone.

In studies of local administration of antimicrobial drugs, there was no significant improvement of clinical parameters after use of FMSRP and chlorhexidine gel in patients who developed diffuse periodontitis and type 2 diabetes with poor glycemic control. There was also no significant improvement of clinical parameters with use of SRP and minocycline gel, compared to SRP alone, in patients who developed periodontitis and type 2 diabetes with poor glycemic control. In contrast, significant improvement in clinical parameters was found using SRP with clarithromycin gel in patients with chronic periodontitis and type 2 diabetes with favorable glycemic control, compared to SRP alone. Similarly, SRP and doxycycline gel produced a significant improvement of clinical parameters in patients with type 1 diabetes, compared to SRP alone.

Based on this evidence, concomitant oral administration of antimicrobial drugs and local administration of tetracyclines or macrolides may be more effective for diffuse periodontitis, but the effects of oral and local antimicrobial drugs may be less effective in patients with periodontitis and diabetes. Therefore, concomitant antimicrobial therapy may be effective in compromised patients with diabetes, and thus the recommendation level was determined to be B (level 1). In the future, comparative studies with a sufficient sample size, the same protocol, and a uniform antimicrobial drug that take into account the severity and expansion of periodontitis as inclusion criteria, glycemic control and BMI (which are important, especially in a study with inflammation markers, rather than clinical parameters, as the endpoint, as explained in CQ1), local and systemic inflammation, and the level of insulin resistance. A study in Japanese subjects suggested that concomitant antimicrobial drugs are effective even if improved glycemic control is used as an outcome, and thus further studies are warranted to establish an effective antimicrobial therapy.

	CQ/Contents	CQ5 Is treatment for bacteremia necessary in basic periodontal treatment for patients with diabetes?
5	Recommendation/response	Bacteremia may be caused by scaling root planing (SRP) in basic periodontal treatment, by a periodontal tissue test with a probe, and by mechanical plaque control such as brushing. However, since bacteremia develops for a short period of time with an extremely low level of invasion, the possibility of diabetes aggravating by this disease is low. Since no reports have suggested that the incidence and severity of bacteremia are higher in patients with diabetes than in healthy persons, and the advantages of decreased inflammation in periodontal tissues are high, no particular countermeasures for bacteremia are necessary.
	Level of recommendation	Grade C: Reasons not clear to recommend.
	Level of evidence	Evidence level: 3[note]
Explanation		Note) Non-randomized comparative study, controlled before-and-after trial, retrospective cohort study, case control study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT Background/objectives: Basic periodontal treatment is performed to remove causes of bacteremia from the oral cavity, and its outcome may affect subsequent periodontal treatment. However, SRP may damage tissues and cause bacterial invasion in the body, as seen in tooth extraction. Such bacterial invasion might also be caused by a periodontal tissue test such as probing and by daily tooth brushing, and bacteremia could develop temporarily. Bacteremia derived from the oral cavity including periodontal tissues is a concern in compromised patients, as the cause of focal infection. For immune-compromised patients with diabetes with local protracted wound healing and prolonged bleeding time, there are concerns about aggravation and development of complications. Explanation: Bacterial invasion of periodontal tissues in SRP and supragingival scaling during periodontal treatment or in a periodontal tissue test with a probe causes the blood endotoxin level to increase, inducing development of bacteremia (level 4). Daily activities including mechanical oral cleaning with brushing and interdental brushing and mastication might also cause bacteremia (level 4). There are no clinical differences in the incidence, severity, and duration between bacteremia caused by dental treatment and those caused by daily activities such as brushing and mastication. In bacteremia caused by dental treatment, the bacteria level is ≤104 colony forming units (CFU) per 1 mL of blood and rapidly decreases in 10-30 min after development, and thus this is

considered to be a biologically less-invasive and temporal disease. However, the incidence of bacteremia caused by scaling is significantly higher in patients with periodontitis than in those with gingivitis and in healthy persons, and the bacteria level is positively correlated with gingival index, plaque index, and the number of positive bleeding sites upon probing. Thus, advanced periodontitis may increase the risk of bacteremia (level 4). Therefore, basic periodontal treatment to improve gum inflammation and maintain oral cleanliness is likely to contribute to prevention of oral cavity-derived bacteremia.

Diabetes tends to be associated with increased susceptibility to infection and protracted wound healing. The migratory capability of leukocytes and the capacity to generate active oxygen may be decreased in host immune function, and careful attention should be paid to development of complications such as bacterial endocarditis because the incidence of bacteremia is increased when the blood glucose level is high. However, the risk of oral cavity-derived bacteremia in patients with diabetes is no higher than that in healthy persons. In a cross-sectional study in patients with type 2 diabetes, there were no significant differences in risks for bacteremia, other than urinary tract infection, in comparison to non-diabetes patients, and no difference in therapeutic results.

Temporal bacteremia may develop after basic periodontal treatment in healthy persons, but there is no high-level evidence for its severity and adverse effects. Patients with diabetes with poor control should obtain opinions from a physician, but the advantages of improvement of periodontal tissue inflammation are greater than the risk of development of bacteremia, even in patients with diabetes, and thus basic periodontal treatment is recommended. However, it is important to maintain favorable glycemic control to avoid unnecessary development of bacteremia. For cases in which invasive surgical treatment may be required due to severe inflammatory symptoms caused by poor control, refer to section CQ8.

	CQ/Contents	CQ6 What level of glycemic control should be achieved in invasive procedures such as periodontal surgery in patients with diabetes?
6	Recommendation/response	There is no standard for glycemic control in open procedures such as dental surgery in patients with diabetes. However, in a study in Japanese patients with diabetes who underwent percutaneous coronary revascularization, the outcomes of patients with HbA1c <6.9% were better than those with HbA1c ≥6.9%. Therefore, in periodontal surgery with relatively low invasiveness, HbA1c around 6.9% can be used as the reference level.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 3[note]
Explanation		Note) Non-randomized comparative study, controlled before-and-after trial, retrospective cohort study, case control study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Postoperative complications are common in patients with diabetes in surgery for cardiac disease. Incidences of postoperative death and complications are particularly high in patients receiving insulin treatment. Patients with diabetes tend to develop infection, and those with poor glycemic control have wider and severer infection. Such patients also tend to develop infection with an increase in blood glucose, which may decrease resistance to the infection, and thus it is important to prevent postoperative complications. For this, there is a need to clarify the level of glycemic control required for periodontal surgery.

Explanation:
There have been no randomized comparative studies on complications (infections) after periodontal surgery in patients with diabetes. In a retrospective cohort study in Japanese subjects, the incidence of infection after coronary artery bypass surgery was significantly higher in patients with diabetes (average HbA1c: 7.1% [NGSP]), compared to non-diabetes patients (average HbA1c: 5.7%). In addition, in the above-mentioned study of outcomes of percutaneous coronary intervention, the incidence of major cardiovascular events in patients with preoperative HbA1c ≥6.9% was significantly higher than that in those with HbA1c <6.9%. However, multivariate analyses in both studies suggested no significant relationship between preoperative HbA1c and development of major cardiovascular events. This may be because patients with diabetes have various |

complications and a difference in disease background might be due to preoperative glycemic control. In a prospective cohort study in Canada, there were no differences in incidences of major complications and infection in

non-diabetes patients and patients with diabetes with HbA1c <6.5%, but these

incidences were significantly higher in patients with diabetes with HbA1c ≥6.5%.

In a report on postoperative outcomes of percutaneous coronary artery intervention, insulin therapy showed a positive correlation with postoperative cardiovascular events, but a negative correlation with biguanide drugs.
In the Training Guidebook for Board Certified Diabetologists edited by the Japan Diabetes Society, a fasting blood glucose level of 100-140 mg/dL and postprandial blood glucose level of 160-200 mg/dL are proposed as targets during surgery or preoperative control in the ICU. In intraoperative management of small-scale surgery, a level of 150-250 mg/dL is the target. Preoperative, intraoperative and postoperative glycemic control are all important to prevent postoperative complications and obtain favorable therapeutic results.
If the standard level of glycemic control in periodontal surgery for patients with

diabetes is based on these reports, preoperative HbA1c should be <6.9%, or

fasting and postprandial blood glucose levels should be 100-140 mg/dL and 160-200 mg/dL, respectively, according to the Training Guidebook for Board Certified Diabetologists. However, since periodontal surgery is less invasive compared to coronary artery surgery, the results above should be considered only as a guide (safety threshold). The targets should not be used in a case in which the merits of a surgical procedure, such as tooth extraction, are expected to be larger than the disadvantages of tooth conservation. In such a case, however, it is important to increase intraoperative blood concentrations of antimicrobial drugs sufficiently by implementing more thorough measures for antimicrobial therapy, as discussed in CQ8.

At present, in Japan, the target HbA1c to prevent complications is <7.0%

(NGSP) and the desired HbA1c for favorable long-term therapeutic outcomes is

<7.0%. In addition, in the Evidence-based Practice Guidelines for Treatment of

Diabetes in Japan 2013 of the Japan Diabetes Society, it is suggested that diabetes specialists should cooperate with other physicians and dentists in treatment of patients who require surgery or treatment for dental caries or infection. Thus, it is desirable to establish a good cooperative relationship with diabetes specialists for periodontal surgery and commencement of periodontal treatment.

	CQ/Contents	CQ7 Should warfarin be suspended when patients with diabetes undergo dental extraction, basic periodontal treatment, or periodontal surgery?
7	Recommendation/response	The risk of events that may be caused by cessation of warfarin is likely to be larger than the risk of bleeding in invasive treatment for patients with continuous administration of the drug. Therefore, it is recommended not to discontinue warfarin for tooth extraction, basic periodontal treatment, and periodontal surgery.
	Level of recommendation	Grade D: Recommended not to perform.
	Level of evidence	Evidence level: 1[note]
Explanation		Note) RCT other than a high-level randomized comparative study, and related meta-analysis or systematic review Background/objectives: Since patients with diabetes have a high risk of circulatory disease, they require stricter management of blood pressure and often receive administration of anticoagulant and antiplatelet drugs to prevent embolization. Warfarin (warfarin potassium) is the most frequently used anticoagulant in Japan, and bleeding may be extended after invasive procedures in patients taking this drug. In 1957, Ziffer et al. recommended suspension of anticoagulants for tooth extraction in patients receiving these drugs because postoperative bleeding developed after tooth extraction in a case with continuous administration of anticoagulant. Since many bleeding events occur during endoscopic treatment or from the digestive tract in patients taking warfarin, suspension or a decrease in the anticoagulant dose has been considered as an option for invasive treatment. In 1963, Marshall et al. reported a case in which cardiac infarction developed after discontinuation of an anticoagulant before tooth extraction, and emphasized the risk of infarction upon drug discontinuation. It was reported that warfarin might show a rebound phenomenon to facilitate clot formation after discontinuation and recommencement, and that thrombosis often developed during suspension of anticoagulants and that serious disease was induced. These cases illustrate the various conflicting opinions on continuous use of anticoagulants for prevention of thrombosis or a decrease or suspension of anticoagulants to avoid postoperative bleeding events in minor oral surgery. Thus, there is a need to establish clear guidelines for tooth extraction or periodontal surgery for patients under treatment with anticoagulants. Explanation: There is no large difference in bleeding after invasive dental procedures with and without continuous administration of warfarin. Since postoperative bleeding can be arrested in most cases by appropriate local procedures, even in patients taking warfarin, it is not recommended to discontinue the drug for scaling, tooth extraction, or periodontal surgical treatment. There is evidence (level 2) for this

conclusion from several randomized comparative studies.

In a literature search, we found two randomized comparative studies on accidents such as postoperative bleeding after continuous administration or discontinuation of warfarin for minor oral surgery. In one study in 214 patients receiving anticoagulants who were scheduled to undergo tooth extraction at a dental department of a hospital in Saudi Arabia, the subjects were randomized into four groups: no suture + discontinuation, no suture + continuation, suture + discontinuation, and suture continuation. There was no difference in postoperative bleeding and wound healing with discontinuation and continuation, although postoperative bleeding was more common in patients with suture (level 1). The second study was a randomized comparative (prospective open-label) study in the dental department of a hospital in Italy in 131 patients under anticoagulant treatment who were scheduled to undergo tooth extraction. The subjects were randomized into groups with decreased or continuous

anticoagulants. Mild postoperative bleeding occurred in 15.1% and 9.2% of

cases in the respective groups, suggesting that there is no need to decrease the anticoagulant dose for normal tooth extraction (level 1). Furthermore, the results of a meta-analysis of a randomized comparative study including level 1 evidence also suggested that continuous administration of anticoagulants in dental surgery including tooth extraction does not increase the risk of postoperative bleeding, compared to decreased or suspended administration (level 1).

Since these studies were not performed in Japanese subjects, there is a concern about the applicability of the results to Japanese people, who have a relatively low incidence of infarction. Regarding this possible ethnic difference, 5 hospital cohort studies (with controls) have been performed in Japanese subjects receiving anticoagulant therapy to compare continuous use and discontinuation of warfarin. All of these studies suggested no differences between continuous and suspended administration of warfarin for tooth extraction (level 3), and thus similar procedures to those used overseas can be used in Japan. The 2010 guidelines announced by the Japanese Society of Dentistry for Medically Compromised Patients, the Japanese Society of Oral and Maxillofacial Surgeons, and the Japanese Society of Gerodontology suggested that no serious bleeding complications occur after tooth extraction with continuous administration of warfarin, if the patient has stable underlying disease, and that the International Normalized Ratio (INR) or PT (prothrombin time)-INR (target international normalized ratio of blood coagulation time calculated based on prothrombin time) had a standard level of 1.0. An increase in this ratio shows increased difficulty in blood clotting, but the ratio was within the therapeutic range (level 1). In addition, a study of periodontal surgery suggested no difference in postoperative bleeding in patients with INR ≤3.0, and thus it is recommended that warfarin should be continued for tooth extraction and periodontal surgery (level 4).

As mentioned above, tooth extraction and periodontal treatment can be performed with continuous administration of warfarin for patients with periodontal disease if INR is ≤3.0, but evidence is not sufficient for periodontal disease. However, since it is often difficult to arrest bleeding after surgery in patients under anticoagulant therapy, compared to healthy persons, careful attention should be paid to minimize invasion as much as possible in surgery, perform appropriately local arrest of bleeding, and remove inflammatory tissues. In addition, it is important to obtain the latest INR level when possible and use sufficient anti-inflammatory procedures before surgical treatment.

	CQ/Contents	CQ8 Should more thorough administration of antimicrobial drugs be used in surgery for patients with diabetes?
8	Recommendation/response	Since the risk of surgical site infection (SSI) after periodontal surgery for patients with diabetes with favorable glycemic control is equivalent to that in healthy persons, there is no need for thorough use of antimicrobial drugs. However, patients with diabetes with poor glycemic control have a risk of infection in surgery, and it is desirable to use preventive administration of antimicrobial drugs before and after surgery.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 3[note]
Explanation		Note) Non-randomized comparative study, controlled before-and-after trial, retrospective cohort study, case control study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Increased susceptibility to infection and protracted wound healing are clinical characteristics of patients with diabetes. Long-term continuous hyperglycemia due to abnormal glycometabolism is known to cause microvascular damage, abnormal collagen metabolism, and mild immunodeficiency, and is generally considered to increase the risk of SSI in surgical procedures.
One patient with diabetes (blood glucose: 305 mg/dL) was reported to have developed clostridium deep neck infection after tooth extraction. A second patient with poor glycemic control developed serious Mucormycosis after tooth extraction. As seen in these cases, patients with diabetes have a higher risk of infection after invasive procedures such as tooth extraction, compared to healthy persons, but there are cases in which such procedures are required. Thus, there is a need to clarify whether thorough chemotherapy is required.

Explanation:
Patients with diabetes with poor glycemic control tend to be infected by bacteria, tubercle bacilli, and fungi, and these infections can easily become serious. However, there are no randomized comparative studies that suggest the need for thorough chemotherapy after surgery for patients with diabetes. In a retrospective observational study, the incidence of infection was significantly decreased after surgery for patients with preoperative HbA1c <7% (NGSP) (level 3), and no special considerations were required for supportive periodontal therapy (SPT) and surgical periodontal treatment if HbA1c is controlled at ≤7.0% (NGSP). In contrast, in total knee arthroplasty for patients with HbA1c ≥6.8% (NGSP), leucocyte count and CRP level in postoperative week (POW) 1 and white blood cell count in POW 2 were significantly elevated, even with preventive |

administration of antimicrobial drugs, suggesting the importance of glycemic control in the perioperative and antimicrobial therapy periods. In a study of SSI risk factors after colectomy in patients with diabetes, postoperative thorough glycemic control and administration of antimicrobial drugs within 24 h after surgery were found to be more important for prevention of postoperative infection, compared to preoperative procedures (level 2). A study of preventive administration of antimicrobial drugs for wound infection after spinal surgery showed that 1-day administration of these drugs could prevent postoperative infection for patients with no complication of diabetes, while antimicrobial drugs were required for 3 days, including the day of surgery, for patients with a complication of diabetes (level 2). Furthermore, in patients with diabetes who underwent spinal instrumentation surgery, the rate of SSI in those with proteinuria (qualitative examination) was 6.28-fold higher than in those with no proteinuria. There was no significant difference in glycemic control (mean HbA1c 7.2% (NGSP)) between these groups, and therefore it was suggested that proteinuria may be a useful index of SSI risk.

These findings suggest the need to examine glycemic control status (HbA1c <7% as a guide) and complications (inadequate blood flow caused by microangiopathy and macroangiopathy) to determine whether thorough use of antimicrobial drugs should be selected for prevention of SSI in patients with diabetes. Indiscriminant excessive administration of antimicrobial drugs for prevention of postoperative infection should be avoided. Since microcirculatory disturbance and poor wound healing are likely when diabetic complications develop due to poor glycemic control, or complications that may be caused by diabetes, such as proteinuria, develop, thorough preventive administration of antimicrobial drugs should be performed immediately before and during surgery. If microcirculatory disturbance due to long-term hyperglycemia is suspected or in a case in which no treatment has been performed for diabetes, cooperation with or introduction to a diabetes specialist is required before surgery.

CQ/Contents	CQ9 Can patients with diabetes obtain therapeutic effects of periodontal guided tissue regeneration equivalent to those in non-diabetes patients?

9	Recommendation/response	There is insufficient evidence for long-term therapeutic results of periodontal regeneration in patients with diabetes. It is not recommended for patients with diabetes with poor glycemic control to receive periodontal regeneration.
	Level of recommendation	Grade D: Recommended not to perform.
	Level of evidence	Evidence level: 4[note]

| Explanation | Note) Cross-sectional study, and case accumulation

Background/objectives:
Periodontal guided tissue regeneration to regenerate tissues destroyed by periodontal disease includes bone transplantation, guided tissue regeneration (GTR), and regeneration with enamel matrix protein (Emdogain). In regenerative therapy, treatment with a scaffold and cytokines is performed in clinical practice and is developing into cell treatment. These regeneration methods are likely to be used for patients with diabetes, but such patients have high risks of protracted wound healing and postoperative infection caused by functional deterioration of leucocytes, decreased collagen metabolic capacity, deteriorated function of fibroblast cells to repair tissues, and poor circulation caused by microcirculatory disturbance. Since patients with diabetes have a high risk of infection, it is important to provide tight plaque control and glycemic control in periodontal treatment. However, there are few comparative reports on responses to periodontal treatment in patients with and without diabetes. Many reports suggest that the response to periodontal treatment is similar in patients with diabetes with favorable glycemic control and non-diabetes patients in short-term observation. In addition, a comparison performed 5 years after basic periodontal treatment showed favorable results at surgical and non-surgical treatment sites in both groups. The subjects in this report continued to visit on a quarterly basis and maintained extremely favorable plaque control, which suggests that patients with diabetes can receive periodontal treatment, including surgical procedures, if they have good maintenance for a long period. However, the response to periodontal regeneration, which requires higher level techniques and active regeneration capacity, is unclear in patients with diabetes. In the current era of growing expectation for regeneration therapy, guidelines for the efficacy of periodontal regeneration for patients with diabetes are necessary.

Explanation:
In a literature search, we found only two case reports of GTR performed in the context of diabetes. Furthermore, these two reports were on the same patient. The first described GTR performed for left mandibular nos. 5 and 7 (sites with severe periodontal disease) in a 57-year-old female with type 2 diabetes that was well controlled with a conventional method. Favorable results were obtained |

for regeneration of alveolar bone on X-ray examination 12 months after surgery. The second report described the clinical course of the same patient at 10 years after the first report (11 years after GTR). She had lowered compliance, no revisits, and redevelopment of periodontal disease caused by poor control of diabetes due to a transition to insulin dependence, aggravated conditions compared to those before GTR, and loss of the two teeth. Based on these findings, it was concluded that GTR is contraindicated in patients with diabetes with poor control.

An animal study on GTR performed as preparative treatment for implantation suggested no difference in neonatal bone between diabetes animals with poor control and non-diabetes control animals, but in a retrospective clinical study on autogenous bone graft for formation of an alveolar ridge in humans, high failure rates were found in patients with diabetes.

Based on these findings, the evidence level of the derived report is low (level 6), and no clear suggestion cannot be made. A speculative recommendation is that periodontal regeneration is contraindicated in patients with diabetes with poor control or with compliance that is likely to decrease.

CQ/Contents	CQ10 Can patients with diabetes obtain therapeutic effects of implant treatment equivalent to those in non-diabetes patients?
10 Recommendation/response	Patients with diabetes with favorable control may obtain therapeutic effects equivalent to those for non-diabetes patients because success and survival rates are high after implantation, but there are some negative reports. Standards of control are unclear in many cases, and thus the treatment cannot be actively recommended.
Level of recommendation	Grade C: Reasons not clear to recommend.
Level of evidence	Evidence level: 3[note)]

Explanation

Note) Non-randomized comparative study, controlled before-and-after trial, retrospective cohort study, case control study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Many reports have discussed the indication and prediction of implant treatment in systemically healthy patients. Patients who request implants for tooth loss caused mainly by periodontal disease include many in late middle age or older who may develop diseases of the elderly. Patients with diabetes generally have considerable tooth loss, and thus require many implants and have a high expectation of treatment. Thus, dentists have increasing opportunities for use of implants in patients with systemic disease. It is reasonable to expect protracted wound healing based on results in animal diabetes models, but osseointegration has been achieved in diabetes and non-diabetes animals. Successful use of implants in patients with other systemic diseases has been reported, but there has been no detailed analysis of implant treatment in patients with diabetes. Therefore, guidelines based on evidence are needed regarding the efficacy and prediction of implant treatment in patients with diabetes.

Explanation:
In a literature search, six reports were found, including 1 clinical review, 3 retrospective cohort studies, 1 case control study, and 1 report on case accumulation. Three systematic reviews were also found. Recent systematic reviews suggest that patients with type 1 and 2 diabetes with favorable glycemic control achieved a high implant survival rate, as seen in non-diabetes patients, in a randomized comparative study, retrospective cohort study, and prospective cohort study. This suggests that implant treatment is not contraindicated in patients with diabetes if glycemic control is favorable. However, since few reports included blood glucose levels and HbA1c, the required level of glycemic control is unclear. The results of each study were evaluated as sufficiently successful or somewhat unsuccessful. This evaluation is satisfactory, but there are reports suggesting that the survival rate of implants in patients with diabetes with favorable control is lower than that in non-diabetes patients, that significantly

higher rates of unsuccessful implant use occurred in patients with type 2 diabetes compared to non-diabetes patients, that patients with diabetes tended to develop peri-implantitis (odds ratio of 1.9 compared to non-diabetes patients in logistic analysis), and that the disease duration of diabetes and length of the implant body are significant predictive factors for unsuccessful implant treatment. Therefore, further studies are needed on use of implants in patients with diabetes, and there is a need to establish clear guidelines based on studies with objective standards for disease type of diabetes, age of onset, disease duration, therapeutic method, and long-term control (HbA1c).

CQ/Contents		CQ11 Does periodontal disease easily redevelop in the period of supportive periodontal therapy (SPT) in patients with diabetes?
11	Recommendation/response	Even during SPT, diabetes is a risk factor for periodontal disease redevelopment, and the risk is especially high in patients with diabetes with poor glycemic control. Thus, it is recommended that patients with diabetes receive sufficient glycemic control and tighter SPT.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: $2^{note)}$
Explanation		Note) Prospective cohort study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Patients with diabetes have reduced function of polymorphonuclear leukocytes, increased collagenase activity, and lower capacity to produce collagen. Those with poor glycemic control more frequently develop alveolar bone resorption and attachment loss due to periodontal disease, compared to those with favorable control. Periodontal disease in patients with diabetes tends to be more severe, and patients may redevelop periodontal disease during SPT after active treatment.

Explanation:
Studies on the relationship between periodontal disease and diabetes clearly suggest that diabetes is a risk factor for periodontal disease. We examined the effects of diabetes on redevelopment of periodontal disease in the SPT period after active periodontal treatment.
Costa et al. investigated redevelopment of periodontitis and tooth loss in a 5-year SPT period after treatment of periodontitis, and found that redevelopment of periodontal disease occurred more frequently in patients with diabetes with poor glycemic control, compared to those with favorable control and non-diabetes patients.
Investigations of risk factors for periodontal disease redevelopment in the SPT period have resulted in an unclear relationship with diabetes, but several reports have suggested that smoking and diabetes are risk factors based on the results of multivariate analysis. In these reports, the odds ratio of diabetes for redevelopment of periodontal disease was 1.9-4.2.
These findings suggest that patients with diabetes with poor control can easily redevelop periodontal disease, even in the SPT period. Therefore, it is important to perform sufficient glycemic control and stricter SPT in these patients. |

CQ/Contents		CQ12 Should the interval of SPT be shorter for patients with diabetes, compared to other patients with periodontal disease?
12	Recommendation/response	Since patients with diabetes have a high risk for periodontal disease, even in the SPT period, it is recommended to shorten the interval of SPT to 3-4 times per year or shorter.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 2[note]
Explanation		Note) Prospective cohort study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Patients with diabetes are at high risk for periodontitis. Thus, thorough control is required, even in the SPT period, after periodontal treatment. Guidelines are needed to determine whether the SPT interval should be shortened to prevent redevelopment of periodontal disease, compared to that for non-diabetes patients.

Explanation:
No randomized comparative study on this issue was found, but there was a forward-looking case control study. By selecting pairs with various matched factors in the cohort, patients were divided into two groups, in which only the SPT interval differed. Investigation of the SPT period over 3 years showed that redevelopment of periodontal disease and tooth loss were lower in patients with an average SPT interval of 3.3 months, compared to those with an interval of 8.1 months.
No other studies on SPT interval in patients with diabetes were found, but risk factors including smoking and diabetes may be involved in redevelopment of periodontal disease in the SPT period. Multivariate analysis gave an odds ratio of diabetes for redevelopment of periodontal disease in the SPT period of 1.9-4.2. Based on this, periodontal disease redevelopment can be predicted using risk factors in the SPT period and the SPT interval can be adjusted.
A retrospective study compared therapeutic effects in a high susceptibility group (HSG) of subjects who did not have diabetes, but were diagnosed with advanced periodontitis and received normal non-surgical periodontal treatment, and a normal group (NG) with normal sensitivity. When SPT mainly with oral cleaning instruction was performed 3-4 times per year and debridement was performed, no aggravation of periodontal disease occurred in the NG group, but significant alveolar bone resorption and attachment loss were observed in the HSG group. This suggests that periodontitis can easily redevelop in patients with high disease sensitivity, even if normal SPT is performed.
Based on these findings, the sensitivity of a patient for onset of periodontal disease can be predicted based on various risk factors, including diabetes. If the risk is high, it is recommended to perform SPT with an interval shorter than the normal interval of 3-4 times per year (interval of 3 or 4 months). |

CQ/Contents	CQ13 What level of glycemic control should be provided to patients with diabetes in the SPT period?

13	Recommendation/response	To prevent redevelopment of periodontitis in the SPT period, glucose should be controlled at as close to the normal level as possible. Even if control is difficult, the risk of periodontitis redevelopment is comparatively low if HbA1c (NGSP) is <7.0%. It is recommended to confirm the glycemic control level and perform thorough SPT depending on the control level.
	Level of recommendation	Grade B: Recommended to perform.
	Level of evidence	Evidence level: 2[note)

| Explanation | Note) Prospective cohort study, related meta-analysis or systematic review, and sub-analysis of prescribed RCT

Background/objectives:
Alveolar bone resorption and attachment loss easily develop due to periodontal disease in patients with diabetes with poor glycemic control, compared to those with favorable control. Thus, to prevent progression of periodontal disease in patients with diabetes, it is important to maintain favorable glycemic control. A target glycemic control level required to prevent redevelopment or progression of periodontal disease should be set in patients with diabetes in the SPT period.

Explanation:
No randomized comparative study of this issue was found. In an epidemiological study, progression of periodontal disease and increased tooth loss were more common in patients with diabetes with poor glycemic control in the SPT period, compared to those with favorable control. In the study, appropriate glycemic control was defined as HbA1c (NGSP) of 6.5%. It is unclear whether there is a dose-response relationship between the HbA1c level and the rate of progression of periodontal disease.
A prospective cohort study in Germany suggested that attachment loss was high in patients with poor glycemic control (HbA1c >7.0%) in type 1 and 2 diabetes.
However, there was no significant difference in attachment loss between healthy persons and patients with diabetes with favorable glycemic control.
Based on these findings, favorable glycemic control should be maintained to prevent redevelopment of periodontal disease. The target level of glycemic control has not been closely examined, but HbA1c (NGSP) <7.0% may have a high risk of redevelopment.
Generally, the goals of diabetes treatment are prevention of progression and development of complications. For this, glucose should be controlled at as close to the normal level as possible, but the level should be determined individually |

based on age and risk of hypoglycemia in actual treatment. The Japan Diabetes Society defined the target of glycemic control as HbA1c (NGSP) <7.0% from a standpoint of complication prevention. This was based on a report suggesting that development or progression of microangiopathy was almost inhibited when HbA1c (NGSP) was <6.9%, and on targets defined in several other countries.

However, the risk of development or progression of macroangiopathy is high in the stage of abnormal glucose tolerance, in which only the postprandial blood glucose level is high. This means that all complications cannot be prevented with a target HbA1c (NGSP) <7.0%.

Based on these findings, it is desirable for the glucose level to be controlled at as close to the normal level as possible to prevent redevelopment of periodontal disease in the SPT period in patients with diabetes. Even if such glycemic control is difficult in individual patients, the risk of periodontal disease redevelopment is relatively low if HbA1c (NGSP) is <7.0%. It is important to confirm the level of glycemic control and estimate the risk of periodontal disease redevelopment at hospital visits. It is recommended to adjust the details and interval of SPT based on data for individual patients.