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Periodontal Complications of Hyperglycemia/Diabetes Mellitus: Epidemiologic Complexity and Clinical Challenge

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Running title
Hyperglycemia & Periodontitis

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Abstract

This report provides a comprehensive overview of the adverse effects of hyperglycemia on the periodontium while combining literature reviews with presentation of original data from two large, population based epidemiologic studies with comprehensive periodontal health assessment.
Emphasis is placed on the exploration of hitherto sparsely reported effects of prediabetes and poorly controlled (uncontrolled) diabetes, in contrast to the umbrella term "diabetes". This is due to the realization that it is not simply having a diagnosis of diabetes that may adversely affect periodontal health. Rather, it is the level (severity) of hyperglycemia that is the determining factor, not the case definition of the diagnosis of diabetes, nor the type of diabetes in question. Importantly, this paper also attempts to estimate, based on existing evidence, the improvements in periodontal probing depth and clinical attachment level that can be expected in people with chronic periodontitis upon successful non-surgical periodontal treatment in people with and without diabetes, respectively. This exploration includes the conduct of new systematic reviews and meta-analyses that allow comparison of such intervention outcomes between people with hyperglycemia versus normoglycemia.
Based on both existing literature and original analyses of population based studies, we try to answer questions such as: Is there a glycated hemoglobin concentration threshold for periodontitis risk? Does short-term periodontal probing depth reduction and clinical attachment level gain after scaling and root planing depend on glycemic control in type 2 diabetes? Are short-term scaling and root planing outcomes in people with hyperglycemia/ diabetes inferior to those in people without diabetes? Do periodontitis patients with diabetes benefit more from the use of adjuvant antibiotics with non-surgical periodontal treatment than people without diabetes? Does hyperglycemia lead to greater tooth loss in patients in long-term post-periodontal treatment maintenance programs?
Throughout this review, we compare our new findings to existing literature and report whether results of these new analyses corroborate, or are in discord with, similar scientific reports in the literature. We also explore the potential role of dental health care professionals in helping patients control the risk factors that are identical for periodontitis and diabetes. Finally, we suggest various topics that still need exploration in future research.

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Diabetes is one of the major risk factors for periodontitis (83). Individuals with diabetes are more likely to have periodontitis with increased severity when their diabetes is uncontrolled or poorly controlled. In this sense, periodontitis is considered nowadays as a complication of diabetes (144). If prediabetes and early diabetes were treated effectively, then the progression of hyperglycemia could be prevented or delayed which may eventually lead to reduced periodontitis progression (183). Aging is associated both with a progressive decline in glucose tolerance and coincidentally with increasing prevalence of periodontitis. Increasing life expectancy predicts an increasing burden of periodontal diseases worldwide with considerable variations between different populations. In 2010, severe periodontitis was the sixth-most prevalent condition, affecting approximately 10.8% or 743 million people worldwide. Between 1990 and 2010, the global age-standardized prevalence of severe periodontitis was estimated to be 11.2% (121). The current pattern of periodontitis reflects distinct risk profiles related to living conditions, environmental and behavioral factors, and oral health care systems, including the implementation of preventive oral health schemes (182).

The World Health Organization estimates that, 422 million adults (8.5% of the population) in the world suffer from diabetes in 2014. Since 1980, this number has quadrupled and the percentage nearly doubled. Diabetes is described as a “serious, chronic disease that occurs either when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces“ (238). The vast majority (90-95%) of these metabolic hyperglycemic diseases is type 2 diabetes mellitus (237). According to the International Diabetes Federation (111):

- North America and the Caribbean have the highest prevalence of diabetes (10.8-14.5%), encompassing 44.3 million. In the US alone, the estimated prevalence increased from about 26 million people in 2010 to 29.3 million in 2015 (30.3 million estimated by the Centers for Disease Control and Prevention (30))
- globally, almost half (46.5%) of all people with diabetes (192.8 million) are unaware of their disease, with more than two-thirds in Africa despite the relatively low prevalence there
- 75% of people with diabetes live in low and middle income countries.

This review that is generally restricted to diabetes type 2, provides an overview for a prediabetes-diabetes-periodontitis nexus, particularly involving uncontrolled diabetes. Especially, the relationships between glycemic state or control and severity of periodontitis, as well as prospects of treatment success in periodontally compromised patients are considered.

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Diabetes thresholds

The generally accepted definitions of categories of glycemic states originate with the American Diabetes Association (7) and the World Health Organization in collaboration with the International Diabetes Federation (238) and are based on measures of fasting plasma glucose, oral glucose tolerance tests, or glycated hemoglobin. For the latter, the thresholds for increased risk of diabetes, also known as prediabetes, are set at 5.7 and 6.4%, with diabetes defined to be present at glycated hemoglobin ≥ 6.5% (47.5 mmol/mol) (7). The glycated hemoglobin level of ≥ 6.5% is especially useful to identify individuals who are at risk for developing late complications of diabetes, such as retinopathy (112). Unknown diabetes may be present in individuals if there is neither a diagnosis nor a relevant medication and the level of glycated hemoglobin is ≥ 6.5% or fasting plasma glucose ≥ 7mmol/L (126mg/dl). Nonetheless, diagnosis of prediabetes on the basis of fasting plasma glucose and oral glucose tolerance tests has shown poor correlation with glycated hemoglobin (16). The diabetes risk increases continuously with glycemic measures such as glycated hemoglobin and becoming disproportionately greater at the higher end of the range.

A large prospective study found that a 5.7% cut point has a sensitivity of 66% and specificity of 88% for the identification of subsequent 6-year diabetes incidence (54). The prevalence of prediabetes is increasing worldwide with concomitant risks of developing diabetes type 2 and subsequently all the potentially fatal, long-term complications attributed to diabetes, especially when poorly controlled (57,106). Individuals identified as having prediabetes are more likely to develop kidney disease or cardiovascular disease and are at higher risk for all-cause mortality compared with those with normal glycated hemoglobin (232).

Natural course of prediabetes and diabetes

Impaired fasting glucose and impaired glucose tolerance represent intermediate stages between normal glucose homeostasis and diabetes mellitus and are predictors for future development of diabetes mellitus and its complications, such as cardiovascular diseases. Although scarcely studied, periodontitis also seems to follow such a course as insulin resistance was observed to predict the incidence of periodontitis (222). Thus, special attention should be paid to individuals at increased risk of developing diabetes (39). During the natural course of developing hyperglycemia, interfering measures during the period of normo-glycemia with concomitant insulin resistance are optimal to prevent further progression (Fig. 1).

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[Fig. 1 about here]

Periodontitis and diabetes

There is strong evidence that periodontitis is associated with diabetes. Not only is glycemic control related to periodontitis in a dose-response manner, the microvascular diabetes complications also show associations with severe periodontitis (176). Thus, since there is a gradated risk between glycated hemoglobin level and other diabetes complications, then such a relation may also exist between glycated hemoglobin and periodontitis and consequently, prediabetes may also represent an elevated risk for developing periodontitis.

If we accept periodontitis as the "sixth complication of diabetes", as it was officially suggested more than two decades ago (144), then the thresholds used for identification and prevention of late diabetic sequelae should also apply for periodontitis. However, as noted by the American Association of Diabetes (7) as well as by an international expert committee (112), the relationship between chronic glycemic levels and the long-term complications of diabetes may be better expressed as a continuum, rather than as a strictly dichotomous relationship with fixed cut-offs.

Notwithstanding this, if we accept an increased risk of periodontitis by diabetes as an established fact, the considerations with respect to probable risk thresholds of glycated hemoglobin should also be practicable for the diabetes-associated risk for periodontitis. Most studies exploring the association between diabetes and periodontitis have unequivocally shown that periodontal measures or periodontitis risk rises disproportionally with increasing levels of glycated hemoglobin. The level of hyperglycemia rather than the diagnosis and etiology of diabetes is associated with periodontitis (22,23,49,83) and the probability of later tooth loss (49). For this reason, it is justified to search for risk groups especially prone to develop severe periodontitis as a consequence of high blood glucose levels or "uncontrolled diabetes." Especially in some subgroups, such as male or elderly patients, the association between uncontrolled diabetes and periodontitis is striking (60,61). The subgroup with "uncontrolled diabetes" comprises subjects with undiagnosed diabetes as well as people with diabetes with poor glycemic control. The underlying reasons are different and may include poor compliance with prescription medications or lifestyle recommendations, failure of effects of medication actually taken, insufficient glucose monitoring, or even medically accepted, but limited metabolic control in the elderly (204).

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Mechanisms explaining the diabetes-periodontitis interaction

Both periodontitis and diabetes are chronic, inflammation driven diseases and often occur in the same individuals and also mutually and adversely affect each other. Risk factors for both diseases include higher age, male sex, minority race or ethnicity, low socioeconomic status, genetic predisposition (mostly for impaired immune/inflammatory responses), smoking, obesity, low physical activity level, and unhealthy diet (23,24,61,83,84). In especially susceptible individuals, bacterial challenge, particularly form the subgingival plaque, induces breakdown of the periodontal soft and hard tissues (17); and these bacteria are also associated with inflammation and insulin resistance (22,50). Conversely, hyperglycemia may influence the subgingival microbiome with subsequent impact on the severity of periodontitis (221).

Both diabetes and periodontitis are associated with enhanced inflammation and impaired immunological responses (27,128). Elevated levels of systemic inflammatory cytokines, such as the interleukin-1Beta and interleukin-6, and the acute-phase inflammatory marker C-reactive protein are consistently observed in diabetes type 2 as well as in periodontitis (142,185). In each case, a systemic inflammatory susceptibility is observed, eventually with an augmented, even though potentially subclinical, responsiveness to inflammatory stimuli. The increase in systemic markers of inflammation in subjects with uncontrolled diabetes is accompanied by a local pro-inflammatory environment in the gingiva (55). Uncontrolled diabetes influences the expression of tissue degrading enzymes in the inflamed gingiva leading to up-regulation of the ratio between metalloproteinase and their inhibitors (18,96).

[Fig. 2 about here]

A two-way association or interaction has been postulated between diabetes and periodontitis assuming that either condition interferes with the other. A somewhat different view may postulate the interaction as a type of vicious circle as exemplified in Fig. 2 (5,97). Chronicity of inflammation presents the strongest plausibility for detrimental effects of deteriorating inflammatory events that could also link periodontal disease to diabetes. In mechanisms underlying the relation between chronic inflammation in diabetes and the link to chronic periodontitis, the cells and mediators of the immune system play a central role (104,210).

Advanced glycation end products are synthesized via non-enzymatic glycation and oxidation of proteins, lipids, and nucleic acids (98). Non-enzymatic glycation is also the mechanism by which the protein

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hemoglobin is glycated and forms glycated hemoglobin (143). The production of advanced glycation end products is particularly enhanced in chronic hyperglycemia, as in diabetes mellitus. Interactions of advanced glycation end products with their receptors and oxidative stress-mediated pathways provide additional links from diabetes to periodontitis (32,135). Thus, the chronic complications of diabetes are mainly a consequence of chronically elevated glucose levels.

The effect of periodontitis on diabetes may be related to the penetration of the host tissues by bacteria or their degradation products, such as lipopolysaccharides from the outer membranes, also called endotoxins or lipoglycans, into the systemic circulation (11,105). Activation of an exaggerated systemic inflammatory response to subgingival bacteria leads to an acute phase protein burst and systemically elevated levels of pro-inflammatory mediators, such as interleukins, tumor necrosis factor alpha, and others which facilitate insulin resistance (1,162). Experimentally, it has been shown that infusion of tumor necrosis factor alpha in volunteers produce a state of systemic inflammation with increased insulin resistance (175). Risk factors contribute to these pathways; especially visceral fat contributes to systemic inflammation (2,139,243). If this hypothesized vicious circle would reflect the pathogenic relationships in some way, then both conditions, diabetes and periodontitis, would reinforce each other. Insulin resistance and markers of systemic inflammation increase gradually in prediabetes ranges of glucose concentrations (191).

The most common type of insulin resistance is associated with the metabolic syndrome, which is also closely related to periodontitis (174). Obesity is a major source of inflammation and is a confounder of the relationship between diabetes and periodontitis. Analyses of National Health and Nutrition Examination Survey data show that biological variation in glycated hemoglobin is positively associated with inflammation, independent of blood glucose concentration and obesity in participants without diabetes (143).

Associations between the chronic activation of the innate immune system and main risk factors of diabetes and periodontitis support the idea of a nexus between both conditions. Age, obesity, sex and gender, smoking, genetic factors, socioeconomic status all may contribute to subclinical inflammation (23,60,184). However, existence of an association provides no evidence for causation. There could be an association superimposed by overlapping risk factors for diabetes and periodontitis, including smoking, obesity, socio-economic status, and life course related adverse fate (23,60). Periodontitis progression is associated with increased glycated hemoglobin concentration, which is similar to that observed for increases in either waist-to-hip ratio or age (48).

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Admittedly, this may be also interpreted in such a way that both diabetes and periodontitis develop in parallel due susceptibility to low grade inflammation. Age related diseases share a pro-inflammatory status, which may be important in the development of chronic diseases such as diabetes and periodontitis (37). Adult height is an indicator of such inflammatory susceptibility developed during life course. Indeed, diabetes as well as periodontitis is associated with body height (157,228).

Prediabetes

Prediabetes is the precursor stage for diabetes mellitus. Prior to the development of type 2 diabetes, glucose levels increase, but are still below the common threshold for diabetes mellitus. According to the American Diabetes Association, people have prediabetes with fasting plasma glucose levels of 100-125mg/dL (5.6-6.9 mmol/L) and/or impaired glucose tolerance with 2-hour values of the oral glucose tolerance test of 140-199 mg/dL (7.8-11.1mmol/L), and/or glycated hemoglobin of 5.7-6.4% (7). Glycated hemoglobin is the test of choice for diagnosis and management of diabetes (85). However glycated hemoglobin is not a sufficiently sensitive or reliable tool for diagnosis of early diabetes/prediabetes (74), as the prevalence of being at high risk for diabetes/prediabetes detected by glycated hemoglobin is only about one-tenth of that by identified by impaired fasting glucose or impaired glucose tolerance (45). Impaired fasting glucose predominantly reflects hepatic insulin sensitivity while impaired glucose tolerance primarily reflects pancreatic beta-cell function (71). Homeostatic Model Assessment is a way to quantify (score) insulin resistance (Homeostatic Model Assessment- Insulin Resistance) and beta-cell function (Homeostatic Model Assessment-Beta) (152).

In 2017, Centers for Disease Control and Prevention estimated, based on data from 2015, that one-third (33.9%) of United States adults aged 18 years or older – with almost half (48.3%) of those aged 65 years or older -- had prediabetes, representing 84 million US adults (30). Almost 9 in 10 (88.4%) were unaware of their hyperglycemia and hence could not take any precautions. The probability that prediabetes progresses to diabetes is high. Without intervention (oral antidiabetic medication or lifestyle modification), 11% of persons with prediabetes and a body mass index $\geq$ 24kg/m^2 ($\geq$ 22 kg/m^2 in Asians) progressed to type 2 diabetes each year during an average of 3 years of follow-up (129). A systematic review based on 16 studies including 44,203 participants described the risk of developing diabetes with 5-year incidences in the range from 9% to 25% for persons with glycated hemoglobin values between 5.5% and 6.0% and from 25% to 50% for persons with glycated hemoglobin values ≥6.0% (242). Moreover, Nathan et al. (171) estimated that up to 70% of individuals with prediabetes will develop diabetes in the future.

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Although diabetes has a gradual onset with blood glucose levels slowly rising over time, cut-off values used for diagnosis of diabetes -- and accordingly the threshold value for prediabetes -- are based on the risk of developing a diabetes related complication. At a glycated hemoglobin cut-off value of 6.5%, the risk for development of diabetic retinopathy increases steeply, independently of macrovascular complications. Diabetic neuropathy has been reported with even lower levels of glycaemia (108). A systematic review that explored lower threshold levels of glycated hemoglobin calculated a substantially increased (5-fold) relative diabetes incidence risk at glycated hemoglobin ranges from 5.5% to 6.0% compared to glycated hemoglobin < 5%, suggesting the use of a glycated hemoglobin threshold of 5.5% to ensure that persons at risk are identified in time to truly benefit from preventive interventions (242). Earlier reviews of hyperglycemia and periodontitis have focused mostly on manifest diabetes mellitus without considering prediabetes. In the following, studies are presented to illuminate this precursor stage of diabetes mellitus as associated with periodontal disease.

Prediabetes and periodontal complications

The level of hyperglycemia rather than the diagnosis and etiology of diabetes is associated with periodontitis (22,23,49,83) and the probability of later tooth loss (49). Based on existing evidence, we attempted to answer the first question: *Does prediabetes impact periodontal health status?*
A final PubMed/MEDLINE search was conducted on September 27, 2017, using the following search strategy: (insulin resistance OR glucose intolerance OR impaired glycaemia OR hyperglycemia OR prediabetes OR early diabetes) AND (periodontal disease OR periodontitis OR periodontal OR tooth loss). The search was limited to 'Humans', 'Adult: 19+ years', 'English' languages, and 'published from January 1980' and resulted in 231 potentially relevant publications that were supplemented by five additional reports identified by hand searching. Eligibility included original studies with clinical or radiographic periodontal assessment and hyperglycemia assessed by stated criteria. Only studies that took into account the effects of potential confounders and we only report results of the fully adjusted -- and weighted, if applicable -- models. Table 1 presents characteristics and findings from the 15 reports, of which two were of longitudinal and 13 or cross-sectional design.

[Table 1 about here]

<u>Longitudinal studies</u>

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In a prospective cohort study, Chiu and colleagues analyzed data from a public screening program of 4,387 initially periodontitis free Taiwanese aged 35-44 years for up to 5 years (35). Originally periodontitis free, 96 of 297 (32.3%) with prediabetes (fasting plasma glucose 100–125mg/dL) versus 1,129 of 4,033 (28.0%) with normal fasting plasma glucose < 100mg/dL) developed periodontitis (Community Periodontal Index ≥ 3). After adjustment for potential confounders, those with baseline prediabetes had 25% higher risk of incident periodontitis (hazard ratio=1.25; 95% confidence interval: 1.00-1.57) compared to those with normal fasting plasma glucose. Also included in the study were 57 individuals with overt diabetes (fasting plasma glucose ≥ 126mg/dL) of whom 22 (38.6%) developed periodontitis and were almost twice more likely to develop periodontitis (hazard ratio=1.95; 95% confidence interval: 1.22-3.13) than the normoglycemic. Hence, a dose response effect was discerned in this study with a gradation in incident periodontitis from no diabetes (28.0%) through prediabetes (32.3%) to manifest diabetes (38.6%).

In a Finnish prospective cohort study among 157 never-smoking adults 30-64 years of age with no periodontal probing depth ≥ 4mm (periodontal pocket) nor diabetes at baseline, 108 (68.8%) of them had developed periodontal pockets about 4 years later (222). When comparing the highest tertile to the lowest tertile of the Homeostatic Model Assessment index, the incidence rate ratio of new periodontal pocket formation was greater among subjects with insulin resistance (Homeostatic Model Assessment-Insulin Resistance, incidence rate ratio=1.7; 95% confidence interval: 1.1-2.7) as well as in individuals with impaired beta-cell function (Homeostatic Model Assessment-Beta, incidence rate ratio=1.6; 95% confidence interval: 1.0-2.6) (222).

Cross-sectional studies

Within a cardiovascular risk study, Benguigui et al. (19) investigated the association between metabolic syndrome, its various components, and gingivitis/periodontitis (gingival index, periodontal probing depth, and clinical attachment level) in a 35-74 year-old population in southwestern France. Participants without diabetes (n=238) in the highest quartile of the Homeostatic Model Assessment-Insulin Resistance index had a significantly increased risk of having a higher prevalence of sites with clinical attachment level ≥4mm, clinical attachment level ≥5mm, and periodontal probing depth ≥4mm compared to those without diabetes in the lowest vs highest quartile in adjusted analyses (risk ratio=1.52, 95% confidence interval: 1.02-2.27), 1.61, (95% confidence interval: 1.00-2.61), and 1.82 (95% confidence interval: 1.08-3.07), respectively.

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Emrich et al. (66) investigated whether diabetes was associated with periodontal destruction by means of clinical attachment level≥5mm and alveolar bone loss in ≥ 15 years old Pima & Papago Indians with diabetes (n=254), a group with prediabetes (impaired glucose tolerance) (n=158), and normal glucose tolerance (n=930). Diabetes and age were significantly correlated to breakdown of periodontal tissues. Subjects with type 2 diabetes had an increased risk of destructive periodontitis with an adjusted odds ratio=2.81 (95% confidence interval: 1.91-4.13) for clinical attachment level and odds ratio=3.43 (95% confidence interval: 2.28-5.16) for severe radiographic bone loss, but no differences were seen between impaired glucose tolerance and normal glucose tolerance for such clinical attachment level and alveolar bone loss.

Genco et al. (84) explored the relationship between obesity and periodontal disease in 12,367 diabetes free US adults aged 20-90 years who participated in National Health and Nutrition Examination Survey III. Participants were stratified by body mass index into overweight (defined as body mass index ≥27 kg/m^2) (n=5,326) and not overweight (n=7,041) and these groups were further stratified into quartiles of insulin resistance expressed as Homeostatic Model Assessment-Insulin Resistance, based on the product of fasting insulin and fasting glucose. Among the overweight US adults, those placing in the highest (4th) Homeostatic Model Assessment-Insulin Resistance quartile had a significantly increased risk for having severe periodontitis with an adjusted odds ratio of 1.48 (95% confidence interval: 1.13-1.93) compared to the overweight participants in the lowest (1st) Homeostatic Model Assessment-Insulin Resistance quartile. On the contrary, the 1st and the 4th quartiles did not differ statistically in non-overweight participants (84).

Hong et al. (109) found an age- and dose-dependent relationship between the presence of diabetes or prediabetes and periodontitis defined as Community Periodontal Index ≥ 3 in a South Korean study comprising 9,977 adults. Participants with prediabetes (fasting plasma glucose 111–125mg/dL) had a 33% increased risk of periodontitis in subjects aged 19 to 39 years and 40 to 64 years, but not in adults 65 years and older. The adjusted weighted prevalence of periodontitis was significantly greater in the groups with prediabetes and diabetes compared with the non-diabetes group in a dose-response fashion with 23.2 (± 1.4)% in impaired fasting glucose (100-110mg/dL) increasing to 29.7 (± 2.7)% in impaired fasting glucose (111-125mg/dL) and to 32.5 (± 2.0)% in manifest diabetes (109).

In a German survey including 3,086 participants, Kowall et al. (131) described a significant relationship between prediabetes and periodontitis (clinical attachment level ≥3mm at ≥2 non-adjacent teeth or mean clinical attachment level, periodontal probing depth), edentulism, or low number of teeth, which however disappeared after adjusting for potential confounders.

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A total of 1,097 adult dental patients in Manhattan, New York (aged 40 years or older if non-Hispanic white and ≥30 years if non-white or Hispanic), who reported to not have diabetes had chairside measures of their glycated hemoglobin values (137). More than one-third (37.3%) turned out to have glycated hemoglobin readings in the prediabetes range (5.7%-6.4%); and they had 26% higher risk for having more teeth with periodontal probing depth ≥5mm and 6% higher risk for missing teeth than the normoglycemic after adjusting for potential confounders.

In another South Korean survey, Lim et al. (140) investigated the association between insulin resistance (scored by Homeostatic Model Assessment-Insulin Resistance) and periodontitis (defined as Community Periodontal Index ≥ 3) in 14,725 adults > 18 years of age. Comparing the insulin resistant with insulin sensitive subjects revealed that only post-menopausal women were more likely to have periodontitis (odds ratio=1.47; 95% confidence interval: 1.07-2.01), but not men or pre-menopausal women. The association was potentiated in overweight post-menopausal women.

In a Japanese case-control study, Marugame et al. (148) examined 664 male military personnel aged 46-57 years and classified them according to their glycemic status in three groups: fasting plasma glucose < 126mg/dL and 2 hour impaired glucose tolerance < 140mg/dL, impaired glucose tolerance (fasting plasma glucose <126mg/dL and 2 hour impaired glucose tolerance 140-199mg/dL, and newly diagnosed diabetes with fasting plasma glucose ≥ 126 mg/dL and/or 2 hour impaired glucose tolerance ≥ 200mg/dL. Neither crude nor adjusted logistic regression models revealed any significant association between impaired glucose tolerance and alveolar bone support or number of sites with bone loss compared to normoglycemia. The study concluded that there is a positive association between type 2 diabetes and alveolar bone loss, but not between impaired glucose tolerance and alveolar bone loss.

Pérez et al. assessed the association between prediabetes and insulin resistance with bleeding on probing and periodontitis according to case definitions developed by the Centers for Disease Control and Prevention and the American Academy of Periodontology for surveillance of periodontitis in a Puerto Rican study including 1,191 overweight or obese 40-65 years old adults without diabetes (181). Adjusted logistic regression revealed a significant relationship between prediabetes and bleeding on probing and severe periodontitis. Insulin resistance was associated with bleeding on probing >30% but not with any level of periodontitis. Impaired fasting glucose was significantly associated with both high levels of bleeding on probing and moderate or severe periodontitis. In contrast, glycated hemoglobin failed to show any significant relationship with high bleeding on probing or periodontitis.

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Among Japanese women aged 40-79 years, Saito et al. (194) compared the 108 with prediabetes to the 435 without hyperglycemia but found no significant association between impaired glucose status and periodontal probing depth or clinical attachment level, respectively, after adjustment.

The third Korean study was based on the same epidemiological data as the study of Lim et al. (140). Song et al. (209) investigated the association between diabetes, prediabetes, and periodontitis (Community Periodontal Index ≥ 3) in 5,690 in mostly obese adults aged ≥ 30 years. The odds ratios for prevalence of severe periodontitis (Community Periodontal Index =4) were significantly increased for the diabetes and prediabetes group respectively compared to healthy subjects after adjustment for 13 confounders. Data comparing the highest quartile of Homeostatic Model Assessment-Insulin Resistance (insulin resistant) with the lowest three quartiles showed that 826 of 1,460 subjects in the highest quartile had manifest diabetes preventing the use of Homeostatic Model Assessment-Insulin Resistance for assessment of prediabetes. Furthermore, only non-obese, but insulin resistant, subjects had an increased risk for severe periodontitis compared to non-obese insulin-sensitive subjects (odds ratio=1.47; 95% confidence interval 1.16–1.87), whereas obese, insulin resistant subjects did not have an elevated risk for severe periodontitis.

The baseline status on which the described longitudinal Finnish study (222) is based was reported as a cross-sectional study (221) that includes 2,050 never-smokers between the ages of 30 and 64 years. Whether defining periodontitis by periodontal probing depth >4mm or periodontal probing depth > 6mm and comparing the highest Homeostatic Model Assessment-Insulin Resistance quintile to the lowest or dichotomizing the Homeostatic Model Assessment-Insulin Resistance values for comparison, no significant associations were identified between prediabetes and periodontitis after adjustment for 7 potential confounders (221).

Zuk et al. (245) analyzed the relationship between diabetes, prediabetes and moderate-to-severe periodontitis with clinical attachment level ≥ 4mm in adults aged 19-79 years using data from the Canadian Health Measure Survey. Only subjects with fasting plasma glucose ≥ 110mg (prediabetes and diabetes) were significantly associated with periodontitis after adjustment for the confounders age, sex, ethnicity, body mass index, smoking, and dental insurance. However, after additional adjustment for income and education, the association with an elevated risk was abolished.

In summary, only two prospective cohort studies that explored the effect of prediabetes on incident periodontitis are available (35,222). Because such studies can yield information on the temporality, namely whether prediabetes or periodontitis existed first, they can providence some evidence regarding which factor (that which existed first) may affect the other, which the cross-sectional studies cannot.

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The two longitudinal studies were conducted in Taiwan (35) and Finland (222), and whereas the former controlled statistically for smoking, the latter excluded smokers. The Taiwanese study analyzed data from a public program screening for 5 chronic diseases and used the Community Periodontal Index, which does not allow estimates of the extent of periodontitis, but only records the most severe periodontal status for an individual. People with any pockets ≥ 4mm (Community Periodontal Index scores 3 or 4) at baseline were excluded, so the new periodontitis cases are those who develop at least 1 pocket ≥ 4mm over 5 years. Moreover, the Community Periodontal Index does not include assessment of clinical attachment level. Hence, the results must be interpreted with caution. The Finnish study reported a statistically significant 70% higher risk for incident periodontitis (defined as development of new periodontal probing depth ≥ 4mm, an inferior measure of periodontitis) in people with insulin resistance (Homeostatic Model Assessment-Insulin Resistance), as well as 60% greater such risk in people with impaired Beta-cell function (Homeostatic Model Assessment-Beta).

Thirteen cross-sectional studies met the inclusion criteria and 12 of them defined periodontitis by a variety of clinical measures, whereas one used panoramic radiographs to score premolars and molars (148). Seven of 13 cross-sectional studies (19,84,109,137,140,181,209) reported significant associations between prediabetes (designated as the exposure) and periodontitis (designated as the outcome). However, these significant associations were strongest in the bivariate analyses, but were attenuated in multivariate models after adjustment for potential confounders, importantly age, smoking, and overweight/obesity. Furthermore, when significant associations were reported, the lower boundaries of the 95% confidence intervals invariably were close to 1, the point at which there is no statistically significant difference between the compared groups. Moreover, most of these significant associations were not identified in the entire study population, but only in specific subgroups, such as those who were overweight (84) or non-abdominally obese (209); post-menopausal (140) or post-menopausal and overweight (140); only the most severe half of those with impaired fasting glucose (111–125mg/dL) (109); and also not for any periodontitis, but only the severe degree (19). Three of the seven studies reporting significant associations were analyses of Korean National Health and Nutrition Examination Survey data from either 2008-2010 (140,209) or 2012-2013 (109), the rest were conducted in France (19), Puerto Rico (181), and the US (84). Of course, a cross-sectional study design is not able to yield information regarding causality.

In conclusion, the two longitudinal and the mostly cross-sectional studies may suggest a tendency for prediabetes to be associated with greater incidence, respective prevalence, or severity of periodontitis,

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irrespective of the applied glycemic and periodontitis case definitions and their corresponding thresholds. A trend for prediabetes contributing to complications for periodontal health in certain subpopulations may exist, but longitudinal studies that apply the same periodontitis and prediabetes case definitions are needed to provide evidence to support such relationship.

Uncontrolled diabetes and periodontal complications

We then attempted to answer the second question based on existing evidence: *"Does poorer glycemic control in type 2 diabetes lead to more severe periodontal complications than better control?" or more broadly: "Is there a dose-response relationship between level of glycemic control in type 2 diabetes and its periodontal complications (incidence or progression of periodontitis, tooth loss)?"*

In order to ensure the ability to determine temporality, only longitudinal, descriptive, epidemiologic studies were eligible for inclusion. Furthermore, only studies that report adjusting for potential confounders were included in order to exclude spurious bivariate descriptive results. Hence, cross-sectional studies, case reports, mechanistic and interventional studies, as well as longitudinal studies that did not adjust their results, were excluded. Studies reporting on type 1 diabetes, a mix of types 1 and 2, gestational diabetes, or diabetes of unknown types were also ineligible. The limit of publication year since 1980 was selected because only more recent (computer based) analyses are able to simultaneously control for several factors. Because these inclusion criteria were relatively strict and it was not always possible to deduct eligibility from the titles and abstracts from searching bibliographic databases, the majority of the literature searching consisted of manually harvesting references from bibliographies from eligible studies, supplemented with searching electronic databases that provided information about later reports that cited them.

Table 2 summarizes the only four studies that met the inclusion criteria. They were published between 1998 and 2012 and were conducted in Germany (49), Japan (169), and the USA (15,217). However, the populations studied cannot be regarded representative for their three continents. For example, the two US studies were conducted among the special groups Pima Indians and Gullah African Americans. Three studies assessed clinical (15,49,169) and one (217) radiographic measures of incidence or progression of periodontitis, and 1 study additionally reported tooth loss (49). The four studies encompassed a total of 8,735 participants, of whom 2,618 had no diabetes and another 5,828 had well-controlled type 2 diabetes, leaving only 289 participants with poorly controlled type 2 diabetes. The studies are highly heterogenic. For instance, the selected glycated hemoglobin threshold values for defining poor glycemic control are 6.5% (169), 7.0% (15,49), and 9.0% (217), respectively. The youngest age of the participants

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ranges from 15 to 34 years, whereas the oldest ranges from 57 to 81 years; and smokers are included in all 4 studies. Even though final models in 3 of the 4 studies adjust for age, and all final models are adjusted for smoking, such differences may still pose difficulties in comparing the studies. Moreover, the studies were conducted among different race/ethnicities, namely African Americans, American Indians, Asians, and Caucasians.

[Table 2 about here]

A total of 88 mostly very heavy Gullah African Americans (78% females, 7% smokers, 5% normal weight/23% overweight/72% obese) initially aged 34 – 77 years in South Carolina were followed between 1.9 and 4.1 (mean: 3) years (15). All non-third molars were probed at 6 sites, totaling 9,648 periodontal probing depth /clinical attachment level sites. Progression of periodontal breakdown (defined as periodontal probing depth $\geq$ 2mm or clinical attachment level $\geq$ 2mm) in those with baseline glycated hemoglobin $\geq$ 7.0% compared to < 7.0% worsened significantly by the baseline worst periodontal probing depth category with both increasing 2-fold in those with baseline 3mm, 2.7-fold in 5mm, and about 3.7-fold in 7mm.

The 5-year Study of Health in Pomerania is by far the largest and most comprehensively designed population study to illustrate the influence of hyperglycemia on periodontitis progression and tooth loss (49). Defining poor control as glycated hemoglobin $\geq$7.0% and good control as glycat ed hemoglobin < 7.0%, those with poor control have greater risk for progression of periodontitis and for losing teeth compared to the normoglycemic, whereas those with well-controlled type 2 diabetes are not at higher risk than those without diabetes. Risks in the poorly controlled group are 4% higher for developing new clinical attachment level $\geq$ 5mm, 36% greater for losing any teeth, and about 60% greater for losing 2 or more teeth. A 1-percentage point glycated hemoglobin increase is associated with a mean increase in periodontal probing depth of 0.04mm and with a mean increase in clinical attachment level of 0.07mm. Importantly, this study demonstrates that it is the hyperglycemia that determines the adverse effects on the periodontium, not the reason for the hyperglycemia or the mere diagnosis of diabetes mellitus.

In a large Japanese population study, Morita and colleagues used the Community Periodontal Index to assess periodontitis, which they defined as scores of 3 or 4 (169). Only 150 among these 30-69-year-old participants were categorized as having poor glycemic control, defined as glycated hemoglobin $\geq$ 6.5%, versus 5,706 with glycated hemoglobin < 6.5%. Those with poor glycemic control had 17% higher risk for

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developing new periodontitis (Community Periodontal Index ≥3) over 5 years, which occurred in 2,068 (35%) of that group.

Finally, panoramic radiographs from 359 Pima Indians aged 15-57 years were scored for new alveolar bone loss occurring over the 2-year study period (range: 1.2 – 6.9 years) (217). Only 7 (4 men, 3 women) participants had poor glycemic control, defined as glycated hemoglobin > 9%, but they had more than 11 times greater risk for developing new alveolar bone loss than the 338 with normal blood glucose. On the contrary, the 14 participants with well-controlled type 2 diabetes were not at higher risk for alveolar bone loss than those without diabetes even when using the high threshold of 9% glycated hemoglobin.

A real-life scenario: examples from the Studies of Health in Pomerania

In order to illustrate the situation more closely, results from two cross-sectional studies from a general Caucasian population are provided as an example. The Study of Health in Pomerania is a population-based prospective cohort study conducted in the northeast region of Germany. Details regarding study design, recruitment, and examination protocols are published elsewhere (107,117). In the first study called Study of Health in Pomerania-0, a total of 4,308 of 6,265 eligible subjects participated in baseline examinations between 1997 and 2001 (117). Another stratified random sample of 8,826 adults aged 20–79 years was drawn for the next study called Study of Health in Pomerania-Trend, in which 4,420 participated between 2008 and 2012 (230). Data from these participants were collected independently of Study of Health in Pomerania-0, but in the same geographic area.

For each of twelve 5-year age strata in Study of Health in Pomerania-Trend, the prevalence of moderate/severe periodontitis was calculated applying the Centers for Disease Control and Prevention and the American Academy of Periodontology case definitions for surveillance of periodontitis (59,179) and depicted in Fig. 3 together with the respective prevalence of prediabetes (glycated hemoglobin 5.7-6.4%) and manifest diabetes (glycated hemoglobin ≥6.5%). Visually comparing the graphs, the prevalence of moderate/severe periodontitis and the prevalence of prediabetes by age group largely coincide from age 40, after which age the prevalence of moderate/severe periodontitis is considerably greater than that of overt diabetes in all age groups.

[Fig. 3 about here]

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Table 3 displays diabetes- and obesity-related measures and their combinations among all study participants and among edentulous only in the two population studies conducted 10 years apart in the same area in Germany (117,230).

[Table 3 about here]

Overall, the mean glycated hemoglobin level of 5.4% was significantly lower in 2008-2012 than ten years earlier (5.5%). Nonetheless, the prevalence of objectively measured diabetes (glycated hemoglobin ≥6.5%) was 10.9% in Study of Health in Pomerania-0 but 12.4% ten years later, a relative increase of 13.8%, with exactly the same relative increase in the self-reported prevalence that increased from 8.1% to 10.5%. Importantly, despite the same increase in objectively and self-assessed diabetes, the proportion of undiagnosed diabetes fell from a quarter (25.7%) in 1997-2001 to only 15.3% ten years later. For comparison, about one-third of the US population aged 20 years and older was unaware of their diabetes as found in National Health and Nutrition Examination Survey 2011-2014 (160), and based on the same data, the Centers for Disease Control and Prevention reported in 2017 that about one-quarter (23.8%) of adults aged 18 years and older with diabetes (11.5%) are undiagnosed (2.7%) (30). The only independent risk factor for being unaware among both US men and women was not having received any health care the last year, which was associated with a 6-fold risk (160). Being of Hispanic ethnicity was a significant factor among US women, but not in men. Due to differences in the health care delivery systems and to the homogenous, Caucasian German population in our study, these reasons do not directly apply to our study.

Obesity -- especially abdominal obesity (waist circumference) -- was also substantially more prevalent in the most recent study and was closely linked to age (not shown) as well as to glycated hemoglobin levels. Almost three-quarters of people with diabetes had a large waist, and more than 60% of people with diabetes -- and 66% of the edentulous among them -- were obese. Total loss of all teeth was significantly associated with glycemia level. Over 10 years, edentulism was reduced by almost half, namely by 46.2%, from 11.7% to 6.3%, but the relationship with the glycated hemoglobin level remained significant. This finding is in accord with the predicted continued decline of the rate of edentulism in the US due to differences among birth cohorts, resulting in the predicted prevalence of edentulism to be 30% lower in 2050 than in 2010 (206). Table 4 presents the distribution of periodontitis, diabetes and risk factors among the different glycated hemoglobin strata for both population cohorts.

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[Table 4 about here]

With increased glycemia, the prevalence of moderate or severe periodontitis classified according to the Centers for Disease Control and Prevention and the American Academy of Periodontitis case definitions (59,179) increased and the number of teeth decreased, both also related to age. An improved state of periodontitis after 10 years is evident in Table 4. While the prevalence of diabetes increased slightly (Table 3), the glycemic control among participants with diabetes improved (Table 4). Compared to the normoglycemic, and in both time periods, those with diabetes (glycated hemoglobin ≥ 6.5%) had almost 3 times higher (2.79) risk for having severe periodontitis and double the risk for having moderate periodontitis.

The probable cause of these differences over the decade elapsing between SHIP-0 and SHIP-Trend emerged when behavioral and socio-economic factors were included and revealed improvements in educational level, hygiene awareness, self-assessment of oral health, and changing use of antidiabetic medications (data not shown).

For comparison to these Study of Health in Pomerania findings, analyses of National Health and Nutrition Examination Survey data for adults 20 years and older revealed a similar increase in the prevalence of prediabetes and unhealthy waist circumferences between 1988/94 and 2012 (145). The 2011-2012 National Health and Nutrition Examination Survey data showed a diabetes prevalence of 12%-14% among United States adults (159), so the prevalence of diabetes had increased, but the proportion of undiagnosed diabetes decreased (200).

Furthermore, the observation of increased diabetes prevalence, but improved metabolic control, is in line with the decline in all diabetes-related complications during two decades in the United States such as acute myocardial infarction, hyperglycemic crises, etc. (92). Thus, it is important for further research to be aware that characteristics of cohorts change with time and, therefore, comparisons with older studies should be made with caution even if identical catchment areas are considered. Most studies compare groups of poorly and well-controlled diabetes -- or groups with hyperglycemia versus healthy (normoglycemic) groups -- and typically find increased risk of periodontitis with elevated glycated hemoglobin, regardless of the selected glycated hemoglobin threshold. This holds true also in the presence of additional risk factors, such as obesity and socio-economic factors.

[Fig. 4 about here]

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As an example from Study of Health in Pomerania-0, the mean clinical attachment level or clinical attachment loss (used as synonyms) is shown across the glycated hemoglobin cut-offs for prediabetes and diabetes in Fig. 4. Risk factors such as these shown here, namely obesity and education, probably exacerbate the severity and extent of periodontitis, but the strong, underlying characteristic, namely the fundamental glycated hemoglobin-dependency, is preserved and reflects the relation as it is true also without these risk factors.

The ultimate objective of all dental preventive and treatment measures is to preserve the patients' teeth and their oral function to preserve or improve their quality of life. The number of teeth lost was assessed in the follow-up studies of Study of Health in Pomerania-0 after five and ten years, respectively. In Fig. 5, the number of teeth lost is shown, adjusted for major risk factors for both diabetes and periodontitis. Again, there is a distinct pattern following the glycated hemoglobin categories even when stratified by obesity. These tooth loss data are in agreement with reports from elsewhere, for instance France (154). Follow-up tooth loss is subject to the same pattern in relation to glycemia state (Fig. 5) as it was shown for cross-sectional clinical attachment level in Fig. 4. When comparing groups of persons, poorer glycemic status is associated with more severe periodontitis.

[Fig. 5 about here]

The individual and the cohort

Hyperglycemia is one of the most important risk factors of periodontitis, as shown by several studies that agree astonishingly consistently (23). But what is the dental care professional to do when a new patient complains of symptoms potentially consistent with periodontitis enters the dental practice? Most published studies that relate periodontitis to glycemic control are studies among groups in which individual participant characteristics are anonymously embedded. In the dental practice, however, the individual patient comes in and has to be treated, so the dentist will be confronted with the special problems of this particular patient to estimate the risk imposed by glycemic control on periodontal destruction. For illustration, Fig. 6 shows the relationship between clinical attachment level and glycated hemoglobin in each individual participating in the two independent cross-sectional studies mentioned.

[Fig. 6 about here]

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Obviously, a risk prediction for a single person regarding the glycemic state and its potential impact on periodontal health seems to be nearly impossible, no matter what risk ratios or odds ratios could be statistically deduced from population group comparisons. Despite the increasing risk with deteriorating glycemic control, cases with severe periodontitis are found within all glycated hemoglobin categories. For example, among the 40-60 years old participants, 25%, 31%, and 36% were categorized as having severe periodontitis in Study of Health in Pomerania-0 at glycated hemoglobin levels < 5.7%, 5.7-6.4%, and ≥ 6.5%, respectively. The corresponding figures 10 years later (Study of Health in Pomerania-Trend) were 19%, 22%, and 25%, respectively.

Individuals with glycated hemoglobin below 6.5% comprise all those who have healthy blood sugar levels, prediabetes, or well-controlled diabetes, whereas the group with glycated hemoglobin levels of 6.5% and greater consists of diabetes patients treated, but not attaining glycated hemoglobin levels below this threshold, as well as those with undiagnosed diabetes.

Thus, instead of considering group-based statistical risk, the frequency distribution of all study participants across the range of glycemia allows appraising the relation between hyperglycemia and periodontitis. Nevertheless, frequency distributions of the population also reveal that the proportion of more severe periodontitis is associated with increasing levels of glycated hemoglobin. This is shown in Fig. 7 with the distribution of individuals by their Centers for Disease Control and Prevention and the American Academy of Periodontology periodontitis classification by glycemic control. For instance, a little more than 100 participants had glycated hemoglobin levels of 4.9% or 5.0% in Study of Health in Pomerania-0. The population-derived frequency distribution of periodontitis grades shows widely overlapping curves. The differences between the periodontitis grades are most substantial within the prediabetes glycated hemoglobin range (5.7-6.4%) or even below. The distribution pattern of the population Study of Health in Pomerania-Trend appears narrower than that of the study ten years earlier due to a diminished number of participants with high glycated hemoglobin levels (see Table 3).

[Fig. 7 about here]

Transforming the histograms shown in Fig. 7 into cumulative frequency distributions reveals that 50% or more of subjects have glycated hemoglobin levels well below 5.7%, irrespective of their periodontitis category (59,179). The glycated hemoglobin medians in no/mild, moderate, and severe periodontitis are 5.0%, 5.2%, and 5.4%, respectively, in this population. For comparison, the 2009-2012 National Health and Nutrition Examination Survey data exposed mean glycated hemoglobin levels of 5.6% and 5.9%,

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respectively, for individuals without and with some form of periodontitis (mild, moderate, or severe) (81).

Because of the close interdependence between glycemic metabolism, obesity, age, and socioeconomic status and their effects on periodontitis, the frequency distributions of confounders are also important. Similar to Fig. 7 that concerns glycemic control, the frequency distribution of three periodontitis severity grades by body mass index as a measure of overweight and obesity is shown in Fig. 8.

[Fig. 8 about here]

Subdividing the glycated hemoglobin frequency distributions (Fig. 7) by important risk factors for both diabetes and periodontitis results in a different pattern. Now, the glycated hemoglobin distribution between participants with no/mild and severe periodontitis are hard to distinguish. The main difference is the relative risk for periodontitis but, no longer the dependence on glycemic level. The no/mild and severe periodontitis frequency distributions by glycated hemoglobin are stratified by 20-age groups (Fig. 9) and education level (< or ≥ 10th grade) (Fig. 10). With increasing age, the distribution moves to higher glycated hemoglobin levels but remains nearly identical between participants with and without periodontitis. In multivariate regression analyses, it was frequently observed that the association between diabetes and periodontitis was attenuated when adjusted for age (131)) or for body mass index (221), for example. This may be better understood by viewing the patterns shown in Fig. 9. Likewise, there is only a small displacement towards higher glycated hemoglobin by the factor education in the distributions between subjects with and without periodontitis, but noticeably more individuals with low education tend to have high glycated hemoglobin. Here, the marked distinction comes from diverging relative risks (61.7% and 19.6% for low and high education, respectively) (Fig. 10).

In summary, results of studies on effects of diabetes/hyperglycemia on periodontitis are confused by two overlapping effects, i.e., the true influence of metabolic disturbance on periodontal inflammation and the differing distributions of subjects with and without periodontitis within a population studied.

[Figs. 9 & 10 about here]

When comparing groups of persons, a poorer glycemic state is associated with more severe periodontitis. This conclusion mentioned above is to supplement with the constraint that the frequency

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distributions imposed by additional risk factors within these groups may overwhelm any influence by hyperglycemia.

Is there a glycated hemoglobin concentration threshold for periodontitis risk?

Suggestions to conduct glycated hemoglobin screening in the dental office setting aim at early identification of hitherto unknown diabetes or even prediabetes. The objective should be to select patients at high risk for developing periodontitis and tooth loss or, by chance, to identify underlying causes of the disease. Step-wise, increasing thresholds were tested to identify a reliable cut-off point separating periodontally affected subjects with glycated hemoglobin above any cut-off from those individuals with glycated hemoglobin below the cut-off value. The proportion with severe periodontitis increased with increasing glycated hemoglobin cut-off levels from glycated hemoglobin ≥5.5% and reached a nearly constant level at 6.5% and greater (Fig. 11). Concomitantly, the proportion with no/mild periodontitis decreases. A nearly constant percentage of moderate periodontitis cases exists at all thresholds. Differences between the two studies ten years apart are obvious. However, the proportion of participants above the glycated hemoglobin thresholds was similar despite the population was ten years apart. As mentioned, there were fewer participants who had glycated hemoglobin levels ≥ 6.5%, and hence, there were smaller numbers of periodontitis cases. Consequently, the confidence intervals increase as seen in Fig. 11, which ultimately diminishes the statistical power to find a significant difference.

[Fig. 11 about here]

However, such high cut-off levels remain significant even in multivariate analyses including demographic factors as it was demonstrated with the 2009-2012 National Health and Nutrition Examination Survey data (81)

There is a continuously increasing portion of periodontitis cases at glycated hemoglobin ≥cut-off with marked difference between both studies. However, in both studies there remain cases of severe periodontitis with glycated hemoglobin below of any chosen cut-off, which are nearly independent of glycated hemoglobin at least when > 6.5%.

The suggested use of the established glycated hemoglobin thresholds as a possibility to detect individuals at risk of periodontitis seems plausible, as higher glycated hemoglobin is associated with higher periodontal probing depth or clinical attachment level measures, necessitating further

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periodontal treatment. However, the continuous risk increase with glycated hemoglobin makes such objective questionable. The population-derived frequency distribution of periodontitis grades according to Centers for Disease Control and Prevention and the American Academy of Periodontology criteria shows widely overlapping curves (Fig. 7). The differences between the periodontitis grades are most substantial within the glycated hemoglobin range defined as prediabetes between 5.7% and 6.4% or even below. If glycated hemoglobin screening should be considered, then identification of patients at risk for periodontitis must be expanded to prediabetes states. This would be a matter of prevention rather than diagnosis as manifest periodontitis occurs with all possible glycemic states.

Treatment options based on bidirectional pathology

The mutual relationship between diabetes and periodontitis spurred doctors on both sides of the scenario, to seek for improvement of periodontal inflammation by adequate blood sugar control or for reduction of glycated hemoglobin by thorough dental treatment. There is low to moderate quality evidence that non-surgical treatment of periodontitis does improve glycemic control in people with diabetes, as concluded by at least 15 systematic reviews with meta-analyses of mostly randomized controlled trials, including a 2015 review by the Cochrane Group (205), as well as 2 umbrella reviews published in 2016 of these meta-analyses (26,72). All these reviews agree that non-surgical periodontal treatment leads to a decrease in glycated hemoglobin 3-4 month post-intervention of between 0.24 and 1.21 percentage point (absolute decrease) glycated hemoglobin. The minimum decrease was calculated from 3 mostly randomized controlled trials (231) and the maximum from 10 mostly randomized controlled trials (213). However, the quality of the included studies is deemed low or low/moderate. The largest randomized clinical trial, the Diabetes and Periodontal Therapy Trial was conducted in the US, cost 18 million US dollars, and reported no reduced level of glycated hemoglobin (68). However, both design, recruitment, and outcome were controversial (25,33,67,161,229).

Regarding the potential effect in the opposite direction, namely improvement of periodontal conditions by improved glycemic control has rarely been studied. Effective metabolic control with glycated hemoglobin decreases is achieved by taking anti-diabetic drugs and lifestyle improvement. Each decrement of glycated hemoglobin is associated with a decrease in diabetes complications, including myocardial infarction and death (99). Thus, the assumption says that any reduction in glycated hemoglobin should also translate into a reduced risk of diabetes-related periodontitis.

The effect of antidiabetic drugs on periodontal conditions is still unclear. Anti-glycemia intervention improved gingivitis, but not periodontitis, as measured by periodontal probing depth or marginal bone

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loss (116,123). It was shown that applying rosiglitazone ameliorates the tissue damage associated with periodontitis only in animal experiments (52,103). Newer antidiabetic drugs, exenatide and sitagliptin, were without effect on alveolar bone loss in periodontally affected rats (167). At least, intensified metabolic treatment with glycated hemoglobin reduction resulted in improved inflammation state characterized by decreased C-reactive protein levels (51). Otherwise, lipid lowering agents such as statins exert an anti-inflammatory effect and may so reduce gingivitis and periodontitis symptoms (9,158). In summary all these drug effects rely on their anti-inflammatory potential rather than on glycated hemoglobin reduction.

Lifestyle interventions such as diet and physical activity are beneficial in reducing the risk of progression from prediabetes to type 2 diabetes mellitus (211). The Diabetes Prevention Program Research Group has published several studies showing that type 2 diabetes may be preventable by diet and exercise (53,225). Future similar studies following such interventions over time could elucidate whether in this way also the onset or progression of periodontitis could be effectively halted, because diabetes and periodontitis share common risk factors and also the measures to prevent them effectively are largely identical (6). This would encompass increasing the awareness in individuals at risk and in health professionals as well as intensive behavioral counselling to promote a healthful diet and increased physical activity. Life style changes targeting both diabetes and periodontitis could interfere with the bidirectional or cyclic interdependence of both conditions (46,134,193).

It should be kept in mind that the duration of diabetes/hyperglycemia exposure is of major influence, though the time lines of mutual disease lengths of diabetes and periodontitis are quite scarcely studied. In diabetes, the duration and age of disease onset are important factors determining the probability of late complications (244). Therefore, not unexpectedly, duration of diabetes is also significantly associated with periodontal health in diabetic individuals (126). Unless people with prediabetes change their lifestyle, most will develop manifest type 2 diabetes within the next years. Lifestyle interventions such as diet and physical activity are beneficial in reducing the risk of progression from prediabetes to type 2 diabetes mellitus. Studies following such interventions over time could elucidate whether also the progression of periodontitis could be effectively halted.

Impact of hyperglycemia (glycemic control) on periodontal treatment outcomes

Background

Diabetes mellitus as a systemic factor affects wound healing via complex pathophysiological mechanisms. Advanced glycation end products under hyperglycemia influence local wound healing.

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Moreover, impaired cell migration and cell proliferation, chronic inflammation, defective innate immunity, impaired angiogenesis, increased oxidative stress, and abnormal expression of matrix metalloproteinases also contribute to impaired local wound healing. Diabetic wounds are accompanied by hypoxia because of insufficient perfusion and angiogenesis (95). Such impairments likely also concern the periodontal wound healing after scaling or flap surgery as well the long-term stability of periodontal conditions.

As shown in the previous paragraphs of this review, epidemiological studies consistently showed that type 2 DM patients with uncontrolled diabetes exhibit more severe periodontitis and more tooth loss than subjects with controlled diabetes. Based on these observations, it was anticipated that periodontal wound healing would occur without problems in subjects with good metabolic control but might be impaired in subjects with uncontrolled diabetes (76).

Citing two 20-year old reports, Lalla & Papapanou (134) state: "With respect to non-surgical periodontal therapy, patients with adequately controlled diabetes can respond well and achieve reduced probing depth and attachment gain (36) ……However, in patients with poor glycemic control, long diabetes duration, and other diabetes complications, response to periodontal therapy appears to be unpredictable as tissue repair and wound healing are compromised (219)."

Both cited groups considered glycated hemoglobin concentration ≤ 8.5% as good glycemic control and glycated hemoglobin ≥ 10% as compromised (poor) glycemic control. The notion that diabetes influences the stability of long-term periodontal results is reflected in risk assessment tools, in which diabetes or systemic diseases are considered predictors for periodontal progression (138). The risk of micro- and macrovascular complications in patients with type 2 diabetes is related to hyperglycemia; and a 1% glycated hemoglobin absolute increase was found to be associated with a 21% increase in clinical diabetes complications (212).

To prevent such complications, the American Diabetes Association recommends as a general target attaining glycated hemoglobin < 7%. However, achievable metabolic control depends on patient attitude, risk of hypoglycemia, comorbidities, life expectancy, etc. The younger the patient, the closer they should attain the target, but some less stringent glycated hemoglobin goals (7.5–8.0% or even slightly higher) are appropriate for older patients with limited life expectancy and comorbidities (113). Since there seems to be no unanimously accepted threshold regarding what constitutes uncontrolled diabetes, we used glycated hemoglobin as a continuous measure in order to explore whether a threshold beyond which periodontal healing is impaired exists. The periodontal community has only limited data illuminating to what extent metabolic control impacts periodontal healing.

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Thus, our first objective was to perform a literature review to evaluate the effects of metabolic control on the reduction of periodontal probing depth and gain in clinical attachment in people with type 2 diabetes and chronic periodontitis after non-surgical scaling and root planing.

It is important for the dentist to know whether to need to be more cautious in performing periodontal procedures in patients with poorly controlled diabetes and whether scaling leads to compromised results with more residual pockets ≥ 4mm, which in turn has to be considered as risk in treatment planning and which may impact long-term periodontal stability. This question was spurred by the discussion about Diabetes and Periodontal Therapy Trial that as mentioned earlier reported no change of glycated hemoglobin following scaling and root planing (68). The critique concerned mainly that because the participants at the end of the study, at the 6 months post-intervention visit, had plaque and periodontal pockets sufficient for them to be eligible for inclusion in the trial from the beginning, the researchers should honestly have concluded that because of the continued plaque accumulation and subsequent inflammation, no conclusion could be made regarding whether successful periodontal treatment would have led to an improvement in glycemic control. Hence, commentaries to this trial asserted that the reported periodontal treatment results were inferior to standard scaling and root planing results, referring to prior treatment results in patients with unknown diabetes status. So the arguments went back and forth, since it is unknown which results should be expected with scaling and root planing and which results are below scaling and root planing standards.

Unfortunately, there are very few comparable studies among subjects with diabetes comparing different levels of metabolic control. Thus, we decided to search for studies that reported baseline values of glycated hemoglobin as well as changes in mean periodontal probing depth and clinical attachment level after non-surgical periodontal treatment with an observation period of at least 3 months. Our first hypothesis was, in brief: the worse the glycemic control, the less periodontal probing depth reduction or attachment gain would occur after scaling and root planing in people with type 2 diabetes, possibly even in a dose-response fashion.

A second objective was to compare the scaling and root planing results in people with diabetes with those in systemically healthy patients. Our hypothesis was that scaling and root planing leads to less periodontal probing depth reduction and attachment gain in people with diabetes compared to systemically healthy patients. Since we could not find a convincing conclusion regarding what may constitute a “good” or “acceptable” result after scaling and root planing, we included studies reporting scaling and root planing results in systemically healthy subjects. Comparison of the studies identified by these two search strategies allowed us to evaluate the impact of glycemic control on periodontal healing

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after scaling and root planing. Since full-mouth scaling vs. quadrant-wise scaling does not render different clinical results according to a 2015 Cochrane review, we included both treatment modalities (56).

We considered studies eligible for inclusion if they were conducted among participants ≥ 35 years of age with chronic periodontitis (as defined by the authors) and with type 2 diabetes (objectives 1 and 2) or without diabetes (objective 2 only), respectively, who received scaling and root planing without use of adjunctive systemic antibiotics or subantimicrobial doxycycline and had no recent history of antibiotic administration, and that reported periodontal probing depth (and eventually clinical attachment level) as patient means

Results

1) *Does short-term periodontal probing depth reduction and clinical attachment level gain after scaling and root planing depend on glycemic control in type 2 diabetes?*

We included 29 randomized clinical trials with 3-months follow-up that reported results from 37 test arm groups comprising 1,089 subjects with type 2 diabetes and periodontal measurements. Several studies reported periodontal findings from two or more groups stratified according to their baseline glycated hemoglobin values and therefore, the number of study groups is greater than the number of included studies. Nine study groups originated in Latin America, 6 in Turkey/Iran, 6 in China/Taiwan, 4 in India, and the rest in Europe, the US, Arab countries, and Japan. Overall, 52.8% of subjects were males and the mean age was 55.0 years. Most cohorts included only nonsmokers. The mean glycated hemoglobin was 7.95% (range 6.0% –10.7%), around 70% of the cohorts reported a diabetes duration with a mean of 9.2 years (range 4.0-17.0 years). The baseline mean periodontal probing depth was 3.2mm (Table 5) and Table 6 exhibits the values for each of the 37 study groups.

[Table 5 about here]

[Table 6 about here]

The mean periodontal probing depth reduction after 3 months was 0.58mm (95% confidence interval: 0.56-0.60) and ranged between 0 and 1.5mm (Fig. 12). The mean clinical attachment level gain in 33 study groups was 0.55mm (95% confidence interval: 0.52-0.58) and ranged from -0.08mm to 1.4mm (Fig. 13). Changes in both mean periodontal probing depth and mean clinical attachment level varied widely across the cohorts as visualized in Figs. 12-13.

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[Fig. 12 about here]

[Fig. 13 about here].

2) Are short-term scaling and root planing outcomes in people with hyperglycemia/diabetes inferior to those in people without diabetes?

For the second question, we included 53 reports including 66 study groups and a total of 1,474 healthy (normoglycemic) subjects that reported scaling and root planing outcomes. The majority of the groups, namely 26 groups, were recruited in Europe, 10 in Latin America, 10 in Turkey/Iran, 7 in India/Pakistan, and 5 in the US. Overall, 49.1% of the subjects were males, and the mean age was 46.5 years.

[Table 7 about here]

In these study groups without diabetes, the mean baseline periodontal probing depth was 3.9 mm (Table 5), and the mean periodontal probing depth reduction was 0.78mm (95% confidence interval: 0.76-0.79) and ranged from 0.08mm to 1.98 mm (Fig. 14). The mean clinical attachment level gain was 0.65mm (95% confidence interval: 0.63-0.67) and ranged between -0.04mm and 1.86mm (Fig. 15). The changes in the means of both periodontal probing depth and clinical attachment level varied widely across the cohorts as seen in Figs. 14-15.

[Fig. 14 about here]

[Fig. 15 about here]

Although the systemically healthy subjects were on average nearly 10 years younger than the participants with diabetes, they had more severe periodontitis as reflected in greater baseline means of periodontal probing depth (3.9mm vs. 3.2mm) and clinical attachment level (3.8mm vs. 3.2mm) (Table 5). Before adjustment for covariates, there was a positive association between greater baseline glycated hemoglobin levels and mean periodontal probing depth both at baseline and after therapy (Fig. 16).

[Fig. 16 about here]

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Even though the mean reduction in both periodontal probing depth and clinical attachment level gain predicted from adjusted meta-regression analyses seemed more pronounced in subjects without diabetes than in subjects with diabetes, this difference did not reach statistical significance. After adjustment for age and sex, no significant associations between baseline glycated hemoglobin and mean periodontal probing depth or its change persisted (Table 8, Model 1).

[Table 8 about here]

On the contrary, each additional mm mean periodontal probing depth at baseline was associated with 0.34 mm reduction in mean periodontal probing depth following scaling and root planing ($p<0.001$; Table 8, Model 2). Regarding clinical attachment level, unadjusted meta-regression analyses demonstrated seemingly higher values of mean clinical attachment level at baseline and after therapy in relation to higher glycated hemoglobin levels. But similarly to the situation with periodontal probing depth, no significant associations between glycated hemoglobin and mean clinical attachment level or its post-treatment change persisted after adjustment for age and sex (Table 9, Model 1), whereas each additional mm mean clinical attachment level at baseline was associated with 0.16mm gain in clinical attachment level following periodontal therapy ($p=0.05$; Table 9, Model 2).

[Table 9 about here]

The presented analyses were calculated with meta-regression tools. It was not possible to adjust the analyses for covariates such as education, smoking, body mass index, etc. because these variables were not available across the studies included.

Comparing participants with diabetes to healthy subjects, baseline values of mean periodontal probing depth and clinical attachment level were strongly correlated with the corresponding measures 3 months after scaling and root planing, irrespective of having diabetes or not. Concomitantly, higher values of mean periodontal probing depth at baseline were associated with greater reductions in mean periodontal probing depth after 3 months (healthy: $p <0.001$, diabetes: $p=0.01$) (Fig. 17). Regarding the shape of the association, no significant differences between systemically healthy and diabetes groups were detected. In similar analyses of mean clinical attachment level, analogous results were obtained (not shown).

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[Fig. 17 about here]

Our first hypothesis that type 2 diabetes with poor glycemic control affects short-term results after scaling and root planing is not supported. At first glance, metabolic control in diabetes patients seemed to impact periodontal probing depth reduction and attachment gain, but this spurious association disappeared when baseline both periodontal measures (periodontal probing depth, clinical attachment level) were taken into account. This is confirmed by the comparison of periodontal probing depth reduction and attachment gain between subjects with and without diabetes: there was no significant difference between the two groups. Hence, our second hypothesis that periodontal patients with diabetes would attain less periodontal probing depth reduction and less clinical attachment gain was also not supported by the evidence. On the contrary, the evidence demonstrated that the main predictor for mean periodontal probing depth reduction or attachment gain is the baseline periodontal status, irrespective of glycemic control. This observation is in line with a meta-analysis comparing scaling and root planing vs. no treatment that did not mention diabetes (226). Wennström & Tomasi reported a mean reduction of periodontal probing depth of 1 to 2 mm and an attachment gain between 0 and 1 mm in sites initially 4-6 mm deep (233). Similar conclusions were presented by Lindhe et al. 35 years ago from a single study (141). The researchers described the initial periodontal probing depth vs. change of attachment with 0.2 (± 0.04)mm attachment gain vs. 1mm increase of initial periodontal probing depth. Their data corroborate quite well with our crude regression slope of 0.16 mm attachment gain with each additional millimeter of initial periodontal probing depth shown in Table 9.

Our meta-regression results are in agreement with previous case series reported by Christgau et al. (n= 3 with baseline glycated hemoglobin >8% (36)) as well as by Westfelt et al. (234) who also did not find a correlation between glycated hemoglobin and change of periodontal probing depth during a 5-year observation period in 20 type 1 or type 2 subjects with diabetes.

As an aside and for the sake of completion, Tervonen & Karjalainen (219) observed impaired short-term healing in 8 type 1 diabetes patients with glycated hemoglobin ≥ 10% and multiple comorbidities. Basic demographic information, such as medical information about drug intake, comorbidities, or duration of diabetes for the individual patient is important to assess to what extent these factors may influence periodontal therapy outcomes. Representative for many authors who did not find any impact of scaling and root planing on glycated hemoglobin, Gay et al. (82) wrote “Non-surgical periodontal therapy… should be considered as a component in the routine medical care of individuals with type 2 diabetes mellitus and periodontitis”, based on a study with a mean glycated hemoglobin level of 9.0%.

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Dentists should not delay non-surgical periodontal therapy in patients with diabetes until good metabolic control is achieved, it should be performed as indicated in patients without diabetes. Averaging whole mouth periodontal probing depth and clinical attachment level underestimates the benefits of scaling and root planing; positive results are more pronounced when analyzing deep pockets. Mean values cannot be translated easily into clinically meaningful data. Since most sites in a patient are shallow or moderately deep, nothing can be said about the clinical significance of these results. There is a wide variation in reduction of mean periodontal probing depth or mean clinical attachment level. The severity of baseline periodontitis varied greatly across the included studies (Figs. 12-15). The more severe the periodontal destruction is, the greater periodontal probing depth reduction or attachment gain can be expected (226).

Short-term periodontal wound healing in people with diabetes seems to be comparable to wound healing in systemically healthy subjects. Local mechanical debridement and improved oral hygiene have more impact on periodontal healing as compared to blood sugar control in a short-term perspective. Through scaling, the biofilm is removed, an active wound is created, and the local mechanism of staged wound healing follows its normal process of hemostasis, inflammation, proliferation, and remodeling (95).

Studies reporting mean clinical attachment level gains or periodontal probing depth reduction below the 95% confidence band as, for example in Fig. 17, fail to attain average expected results. This may be due to patient selection, patient handling, thoroughness of scaling, carefulness of the operator, etc. Coming back to the discussion with respect to the results of the Diabetes and Periodontal Therapy Trial (68), it can be concluded that the reported periodontal probing depth reduction is at the lower end of what represents standard care (205).

Periodontal treatment with adjunctive systemic antibiotics of people with diabetes

Any successful periodontal therapy aims at a gain in clinical attachment level and a reduction in periodontal probing depth. Resolution of periodontal pockets to a state of healthy sulci is regarded the ultimate goal in periodontal treatment. Especially in patients with diabetes and periodontitis, the oral infection may add to dysregulated glycemic control and residual pockets may increase the risk of further attachment loss and eventually to tooth loss (48,50). A 2015 meta-analysis exploring the effect of adjunctive antibiotics in the treatment of chronic periodontitis showed that systemic antibiotic intake combined with scaling offered some additional clinical improvement of periodontal probing depth reduction compared to scaling and root planing alone, but there was no benefit in attachment gain

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(125). Thus the question arose regarding whether a patient with diabetes benefits more from systemic antibiotics than a systemically healthy patient, because scaling alone may be insufficient to achieve a microbial profile compatible with periodontal health in subjects with diabetes (150). Recently, two meta-analyses addressed this question, one was based on 13 (93) and the other on 5 studies (196). Both meta-analyses reported that scaling and root planing with adjunctive antibiotic therapy attained more periodontal probing depth reduction but not attachment gain than scaling and root planing alone. The mean difference in periodontal probing depth reduction between test and control groups was 0.15 mm (95% confidence interval: 0.24-0.06) (93) or 0.22mm (95% confidence interval: 0.34-0.11) (196), respectively. In a sub-analysis based on 3 publications specifically reporting results from patients with uncontrolled diabetes (glycated hemoglobin range 8.3%-10.6%), the periodontal probing depth reduction was 0.26mm (95% confidence interval: 0.39-0.13) greater and the clinical attachment gain 0.26 mm (95% confidence interval: 0.46-0.05) higher in those taking systemic antibiotics vs. controls (196).

A meta-analysis published in 2016 compared the effect of scaling and root planing vs. scaling and root planing with local antimicrobial treatment in patients with chronic periodontitis and diabetes (192). Only in patients with well-controlled, but not in those with uncontrolled diabetes, greater periodontal probing depth reduction and attachment gain were achieved in the scaling and root planing with adjuvant locally delivered antimicrobials, especially in deep pockets.

The prescription of adjunctive systemic antibiotics must take into consideration whether the clinical benefit of marginally more periodontal probing depth reduction outweighs the potential side effects. The decision should be based on individual periodontal destruction severity and be restricted to the most severe cases. This is in line with current recommendations for treatment of patients with chronic periodontitis (102,125,207).

Long-term periodontal maintenance of patients with type 2 diabetes

As shown in the foregoing, short-term scaling results do not seem to be influenced by the degree of metabolic control. However, these studies lasted just 3 months. Periodontal long-term results ≥5 years showed a tendency for the attained periodontal probing depth reduction and attachment gain to relapse with time (118,130). Unanimously, cohort studies report male sex, socio-economic status, smoking, and diabetes mellitus as predictors for periodontitis progression and tooth loss (134). Unfortunately, only one long-term study is available that reports the influence of glycemic control on treated periodontal patients. In a prospective clinical cohort periodontal results were assessed during a

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5-year follow up of 238 participants (43). From this pool, 23 patients with poorly controlled diabetes [glycated hemoglobin=9.1 (± 1.4%)], 23 with well-controlled diabetes [glycated hemoglobin=6.1 (± 0.4%)], and 46 without diabetes (fasting plasma glucose < 126mg/dL, annually) were selected while matching for age and sex (44). Educational background, smoking, diabetes duration, supragingival plaque control, and frequency of maintenance visits were comparable among the three groups. Poorly controlled diabetes patients had statistically more pockets ≥5mm and clinical attachment level ≥ 5mm and had also lost more teeth than patients with well-controlled diabetes or metabolically healthy patients (Fig. 18).

[Fig. 18 about here]

In analyses adjusted for ten potential confounders, patients with poorly controlled diabetes were found to have 3-fold higher risk for further periodontal breakdown (odds ratio=2.9, 95% confidence interval: 1.43-9.81) as well as for losing teeth (odds ratio=3.1; 95% confidence interval: 1.03-10.89), whereas those with glycated hemoglobin < 6.5% experienced no higher risk than the normoglycemic.

Primarily based on epidemiological data, diabetes, especially poorly- or uncontrolled diabetes, has been regarded as risk factor for periodontitis and tooth loss for decades by the periodontal community, but there is a dearth of data to illuminate whether this holds true for intervention studies as well. A total of 17 retrospective studies published the last two decades have evaluated predictors for tooth loss as and outcome in multivariate analyses in patients during periodontal maintenance (Table 10).

[Table 10 about here]

All but one study included information on smoking, whereas 8 of 17 studies did not report diabetes as a predictor. In contrast to smoking, diabetes was a significant predictor for tooth loss in only two out of six studies conducting multivariate analyses. It seems that in many routinely used medical history recordings on which retrospective studies rely, diabetes was not included, possibly because the dentist omitted to ask or to record such health issue, because diabetes did not seem to impose any therapeutic long-term problem. Explanations for this unexpected finding may be that the studies were underpowered to detect small effects of diabetes or that a diagnosis of diabetes did not imposed any problem in periodontal maintenance (see paragraph above). Some studies may have included only participants with controlled diabetes since people with uncontrolled diabetes might seek dental care too

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rarely (69). As well, diabetes mellitus was a rather rare disease until a few decades ago, and still is in some western countries such as in Scandinavia. For instance, the prevalence of diabetes in Denmark was only about 3% in the year 2000, but increased to 5% in 2011, mostly due to the influx of immigrants (8,91). This illustrates that just a short time ago, dentists did not need to know about treating patients with diabetes as much as they do now.

In patients with chronic periodontitis and diabetes, scaling and root planing is an effective treatment in reducing periodontal probing depth and improving the clinical attachment level, irrespective of metabolic control during short follow up duration. The question has yet to be answered by the dental profession to understand the impact of diabetes/hyperglycemia on treatment planning and maintenance in a long-term perspective.

Essential Findings and Conclusions

The prevalence and incidence of prediabetes and type 2 diabetes is increasing worldwide (57). Prediabetes increases the risk of developing diabetes. In industrialized countries, metabolic control seems to improve and most patients are now well controlled. The studies presented provide some evidence that prediabetes is associated with initial periodontal alterations, but not with tooth loss. The 2 longitudinal and 6 of 12 cross-sectional studies report a statistically significant association between prediabetes and periodontitis incidence or prevalence. Variations in the diagnosis of prediabetes are obvious due to different glucose metabolism measures, such as glycated hemoglobin, fasting plasma glucose, impaired fasting glucose, impaired glucose tolerance, Homeostatic Model Assessment-Insulin Resistance, Homeostatic Model Assessment-Beta, and oral glucose tolerance test.

The true threshold for what constitutes uncontrolled diabetes with respect to periodontitis is not known, but uncontrolled diabetes as defined by the reported studies seems to impact periodontal progression and tooth loss.

Resolution of pockets is independent of metabolic control in the short term. Adjuvant systemic administration of antibiotic drugs improves pocket closure but not attachment gain in patients with diabetes. Any decision to prescribe antibiotics depends upon severity of periodontal destruction and the inflammatory status rather than metabolic control.

The duration of both diabetes and chronic periodontitis is mostly unknown and so is their mutual influence and interaction. Life course may determine later chronic disease risk in both diabetes and periodontitis. To promote healthy ageing, studies on those interactions as well as their interactions with environmental factors will be important with implications for public health.

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Increasing life expectancy means that the prevalence of diabetes will likely continue to rise and so will the prevalence of periodontitis as an increasingly greater proportion of the older adults keep their teeth longer. Secular trends influence to a large extent the nexus diabetes-periodontitis. Conclusions based on distinct studies may not be meaningful in other time/geographical circumstances. Older data may reflect a more "natural history" because of less medical intervention, potential patients had very different risk profiles, etc.

Glycemia thresholds for risk prediction of complications are valuable tools in preventing long-term sequelae of diabetes. For the diabetes-periodontitis nexus, the glycemic threshold for assessing the risk imposed by elevated insulin resistance and hyperglycemia for impacting periodontitis is not known.

A great deal of attention should be targeted at risk factors for diabetes and periodontitis, which are largely identical (23,60), such as smoking, obesity, sedentary life-style, etc. Nowadays, dentists start to discuss the utility of health education with respect to diabetes and prediabetes to facilitate the prevention of both diabetes and periodontal complications. Programs including counselling on diet, physical activity, socio-environmental conditions, and self-awareness in health are important issues. In a randomized clinical trial, Lalla and colleagues (136) were able to show that both basic information and enhanced controlled interventions resulted in a significant reduction of glycated hemoglobin in predominantly prediabetes patients already after six months, suggesting that education by dental professionals may contribute to improve the health of patients with, or at-risk for, diabetes. Control of glycemic status may be used as an appropriate tool for monitoring the general metabolic status. There have been claims for many years that efforts aimed at educating patients with diabetes directly to change attitude and behavior in the desirable direction can work in diabetes, however, the evidence for any efficacy when provided in periodontists' or general practitioners' office settings is poor.

While evidence deduced from epidemiological studies can support best clinical practice, it needs to be placed in context of all the conditions of a specific patient. It has to be reflected for the clinical practice whether the focus has to change from the statistical risk considerations towards an assessment and judgment of the individual patient's personal situation. In this respect, personalized medicine is imperative and has always been the intent of dentists in treating patients. Thus, the challenge of the dentist or hygienist with an individual patient is to make a decision. Should this decision be guided by the science of probability (risk of periodontitis due to prediabetes or diabetes), by the art of clinical judgment, or by both?

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Figure Legends

Fig. 1. Natural history of diabetes, schematic outline. The vertical arrow indicates the condition of normoglycemia with insulin resistance, during which period measures to prevent development of diabetes and periodontitis may be optimal and particularly promising.
Footnote: IFG: impaired fasting glucose; IGT: impaired glucose tolerance; IR: insulin resistance,

Fig. 2. Conceptual model connecting diabetes with periodontitis showing possible pathogenic factors and risk factors.
Footnote: AGEs: advanced glycation end products; Il: interleukin; LPS: lipopolysaccharides; ROS: reactive oxygen species

Fig. 3. Prevalence of prediabetes (HbA1c 5.7-6.4%), moderate/severe periodontitis (59,179), and diabetes (HbA1c ≥6.5%) by 5-year age groups. Study of Health in Pomerania-Trend, N=3,343.
Footnote: HbA1c: glycated hemoglobin

Fig. 4. Mean clinical attachment loss by obesity and education in normoglycemia (glycated hemoglobin <5.7%), pre-diabetes (glycated hemoglobin 5.7-6.4%), and diabetes (glycated hemoglobin ≥6.5%). Study of Health in Pomerania-0, crude data, N=3,410.
Footnote: 10th grade: 10th grade of school education; BMI: body mass index; HbA1c: glycated hemoglobin

Fig. 5. Predicted mean number of teeth lost during 5 and 11 years of follow-up, by obesity and glycemic control: normoglycemia (glycated hemoglobin <5.7%), pre-diabetes (glycated hemoglobin 5.7-6.4%), and diabetes (glycated hemoglobin ≥6.5%), upon adjustment for age, sex, education, and obesity. Study of Health in Pomerania-0 at 5 years (N=3,300) and 11 years (N=2,323).
Footnote: BMI: body mass index; HbA1c: glycated hemoglobin; SHIP: Study of Health in Pomerania

Fig. 6. Distribution of mean attachment loss by HbA1c in each individual participant in the two population studies SHIP-0 (1997-2001) and SHIP-Trend (2008-2012). Yellow indicates

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normoglycemia (glycated hemoglobin <5.7%); green prediabetes (glycated hemoglobin 5.7%-6.4%), and dark blue diabetes (glycated hemoglobin >6.5%). Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: HbA1c: glycated hemoglobin; SHIP: Study of Health in Pomerania

Fig. 7. Distribution of study participants according their periodontitis classification as no/mild, moderate, or severe (59,179) by glycemic control (HbA1c) in Study of Health in Pomerania-0 (1997-2001) and Study of Health in Pomerania-Trend (2008-2012). The dotted and dashed lines indicate HbA1c thresholds of 5.7% and 6.5%, respectively. Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: HbA1c: glycated hemoglobin; No.: number; SHIP: Study of Health in Pomerania

Fig. 8. Distribution of study participants according their periodontitis classification (59,179) as no/mild (orange), moderate (olive green), or severe (dark cyan), by level of obesity (BMI). The dashed vertical lines indicate the body mass index thresholds of 25kg/m^2 and 30kg/m^2. Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: BMI: body mass index; No.: number; SHIP: Study of Health in Pomerania

Fig. 9. Age-stratified distribution of study participants with periodontitis categories (59,179) no/mild (orange) or severe (dark cyan) by level of glycemic control (HbA1c). The dotted and dashed lines indicate HbA1c thresholds of 5.7% and 6.5%, respectively. Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: HbA1c: glycated hemoglobin; No.: number

Fig. 10. Education-stratified distribution of study participants with periodontitis categories (59,179) no/mild (orange) or severe (dark cyan) by level of glycemic control.The dotted and dashed lines indicate glycated hemoglobin thresholds of 5.7% and 6.5%, respectively. Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: HbA1c: glycated hemoglobin; No.: number

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Fig. 11. Testing consecutive glycated hemoglobin values as potential cut-off points for the prevalence of no/mild (orange), moderate (olive green), and severe (dark cyan) periodontitis categories (59,179): At each glycated hemoglobin level tested, the proportion with the three periodontitis case categories at or greater than that HbA1c level is shown. The arrows mark the glycated hemoglobin thresholds 5.7% and 6.5%; the vertical bars show the 95% confidence intervals. Study of Health in Pomerania-0, N=3,410; Study of Health in Pomerania-Trend, N= 3,343.
Footnote: HbA1c: glycated hemoglobin; SHIP: Study of Health in Pomerania

Fig. 12. Reduction of mean periodontal probing depth at 3 months after scaling and root planing in patients with diabetes mellitus based on 37 groups comprising a total of 1,089 subjects. The study weights are proportional to the precision of each group estimate (calculated as the inverse of its squared within-study standard error). Please, see Table 6 for sources.
Footnote: CI: confidential interval; ES: estimate in millimeter; year: year of publication

Fig. 13. Reduction of mean clinical attachment level at 3 months after scaling and root planing in patients with diabetes mellitus based on 33 groups comprising a total of 1,009 subjects. The study weights are proportional to the precision of each group estimate (calculated as the inverse of its squared within-study standard error). Please, see Table 6 for sources.
Footnote: CI: confidential interval; ES: estimate in millimeter; year: year of publication

Fig. 14. Reduction of mean periodontal probing depth at 3 months after scaling and root planing in systemically healthy patients based on 66 groups comprising a total number of 1,474 subjects. The study weights are proportional to the precision of each group estimate (calculated as the inverse of its squared within-study standard error). Please, see Table 7 for sources.
Footnote: CI: confidential interval; ES: estimate in millimeter; year: year of publication

Fig. 15. Reduction of mean clinical attachment level at 3 months after scaling and root planing in systemically healthy patients based on 54 groups comprising a total of 1,220 subjects. The study weights are proportional to the precision of each group estimate (calculated as the inverse of its squared within-study standard error). Please, see Table 7 for sources.
Footnote: CI: confidential interval; ES: estimate in millimeter; year: year of publication

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Fig. 16. Mean periodontal probing depth before (blue) and after (red) scaling and root planing by baseline glycated hemoglobin concentration in study groups with diabetes based on 29 reports comprising 37 study groups involving 1,089 subjects. The circle sizes represent the respective study sizes. The study weights for regression are proportional to the precision of each group estimate. Please, see Table 6 for sources.

Footnote: HbA1c: glycated hemoglobin; PPD: periodontal probing depth

Fig. 17. Reduction in mean periodontal probing depth by mean baseline periodontal probing depth (upper panel) and gain in mean clinical attachment level by mean baseline clinical attachment level (lower panel) 3 months after scaling and root planing in normoglycemia and in hyperglycemia/diabetes, respectively. The circles sizes represent the respective study sizes. The study weights for regression are proportional to the precision of each group estimate. Please see Tables 6-7 and Figs. 12-15 for sources.

Footnote: CAL: clinical attachment level; PPD: periodontal probing depth

Fig. 18. Proportion of sites with clinical attachment level ≥5mm or periodontal probing depth ≥5mm, and number of natural teeth present after 5 years of 4-6 monthly follow-up maintenance therapy visits after initial treatment for moderate/severe periodontitis in sex- and age-matched patients without diabetes (fasting plasma glucose <126 mg/dL, n=46), and with well-controlled (glycated hemoglobin <6.5%, n=23) or poorly controlled (glycated hemoglobin ≥6.5%, n=23) type 2 diabetes, respectively (44).

Footnote: CAL: clinical attachment level; PPD: periodontal probing depth

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Table 1. Effect of prediabetes on periodontitis: studies reporting multivariate findings adjusted for potential confounders as of September 27, 2017

Author(s), Year, Country, (Reference #), Duration, Name of Study	A) Total # Subjects (%M): a. PreDM b. Normo-glycemic B) Age range	Exposure Measures: Prediabetes	Outcome Measures: Periodontitis	Risk for Periodontitis* HR/IRR/OR/RR (95% CI)	#: Confounders Controlled
Longitudinal studies					
Chiu et al. 2015 Taiwan (26) 5 years KCIS 2003-2008	A) N=4,387 (≈32%M) no PerioDz a. n=297 b. n=4,033 B) 35-44 years	FPG	Incident PerioDz: CPI≥3	**HR=1.25 (1.00-1.57)**	12: Ag, Al, Be, Ch, E, Fi, H, Ph, Se, Sm, Tr, W
Timonen et al. 2013 Finland (153) 4 years Health 2000 Survey: Follow-up Study on Finnish Adults' Oral Health 2004-2005	A) N=157 (27%M) normo-glycemic, no PerioDz 1) a. n=44(11M/33F) HOMA-IR Q3 b. n=58(12M/46F) HOMA-IR Q1 2) a. n=56(11M/45F) HOMA-B Q3 b. n=49(14M/35F) HOMA B Q1 B) 30-64 years	1)HOMA-IR 2)HOMA-B	Incident PerioDz: PPD≥4mm	1) **IRR=1.7 (1.1-2.7)** 2) IRR=1.6 (1.0-2.6)	7: Ag, B, De, E, PI, Se, To
Cross-sectional studies					
Benguigui et al. 2010 France (13) MONA LISA 2006-2007	A) N=255(55%M); n=238 no DM a. HOMA-IR Q4 b. HOMA-IR Q1 B) 35-74	HOMA-IR	1) PPD ≥4mm 2) CAL ≥4mm	1) **RR=1.61 (1.00-2.61)** 2) **RR=1.52 (1.02-2.27)**	7: Ag, Al, C, CR, E, PI, Se, Sm
Emrich et al. 1991 USA (47) Pima & Papago	A) N=1,342 (43%M) a. n=158 (46M/112F) b. n=930 (432M/498F)	IGT	1) CAL≥5mm 2) ABL≥25%	1) OR: ns 2) OR: ns	7: Ag, BOP, D, Fl, PI, Se,

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Indians 1983	B) ≥15 years				T
Genco et al. 2005 USA (60) NHANES 1988-1994	A) N=12,367 no DM (53%M) A1) BMI≥27: n=5,326 a. IR Q4 b. IR Q1 A2) BMI<27: n=7,041 a. IR Q4 b. IR Q1 B) 20-90 years	IR	Severe PerioDz: mean CAL≥1.5mm	Q4 vs Q1: A1) **OR=1.48 (1.13-1.93)** A2) OR ns	6: Ag, E, I, R, Se , Sm
Hong et al. 2016 South Korea (77) KNHANES 2012-2013	A) N=9,977 no DM (51%M) a1. IFG1: n=1,551 a2. IFG2: n=575 b1. NFG1(<90mg/dL): n=3,107 b2. NFG2 (90-99mg/dL): n=3,701 B) ≥19 years	1) IFG1: 100–110 mg/dL) 2) IFG2: 111–125 mg/dL	PerioDz: CPI≥3 Severe PerioDz: CPI=4	Compared to NFG1: PerioDz 1) IFG1: OR ns 2) IFG2: **OR=1.33 (1.01-1.75)** Severe PerioDz: 1) IFG1: OR ns 2) IFG2: OR ns	10: Ag, Al, CH, E, H, I, Se, Sm, Tr, W
Kowall et al. 2015 Germany (92) SHIP-Trend 2008-2012	A) N=3,086 (49%M) a. n=576 b. n=2,154 B) 20-82 years	1) IGT 2) FPG 3) HbA1c	I) PerioDz: i) EWP ii) PPD iii) CAL II) # teeth	Perio Dz; # teeth: I) [1), 2), or 3)] by [i), ii), or iii)]: OR ns II): OR ns	9: Ag, Al, B, CH, CT, E, Se, Sm, Tr
Lamster et al. 2014 USA (96) 2009-2010	A) N=1,097 (36%M) unknown DM a. n=409 (130M/279F) b. n=603 (229M/374F) B) ≥40y white, non-Hispanic; ≥30y non-white/Hispanic	FPG HbA1c	1) % teeth w/ PPD ≥5mm 2) missing teeth	1) **OR=1.26 (n/a-n/a; p=0.002)** 2) **RR=1.06 (n/a-n/a; p=0.034)**	7: Ag, B, CT, N, R, Se, Sm
Lim et al. 2014 South Korea (99) KNHANES 2008-2010	A) 14,725 (48%M) no DM a. HOMA-IR Q4 b. HOMA-IR Q1 B) ≥19 years	HOMA-IR	PerioDz: CPI≥3	Q4 *vs* Q1: i) post-menopausal F: i.1) all (n=3,223): **OR=1.47 (1.07–2.01)**	10: Ag, Al, E, F, I, Ph, Sm, Tl, To, Y

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				i.2) BMI≥25 (n=1,084): OR=1.92 (1.29-2.87) ii) pre-menopausal F (n=4,442): OR ns iii) M (n=7060): OR ns	
Marugame et al. 2003 Japan (106) 1997-2000	A) N=664 (100%M) no DM a. IGT: n=123 M b. NGT+IFG: n=495 (495M/0F) B) 46-57 years	FPG	ABL (Pano): 1) mean % (pre-)molars only 2) # sites	1) OR ns 2) OR ns	10: Al, B, CH, CT, O, PT, So, Sm, To, Tr
Perez et al. 2017 Puerto Rico (130) SOALS 2011	A) N=1,191 (27%M) no DM a1. FPG a2. IGT a3.HOMA-IR a4. HbA1c 5.7-6.4% B) 40-65 years	FPG IGT HOMA-IR HbA1c	PerioDz (CDC/AAP): 1) moderate 2) severe	a1: 1) OR ns 2) **OR=1.67 (1.17-2.4)** a2: 1) & 2) OR ns a3: 1) & 2) OR ns a4: 1) & 2) OR ns	9: Ag, Al, CH, E, Ph, PI, Se, Sm, W
Saito et al. 2005 Japan (138) Hisayama Study 1988	A) N=583 (0%M) a. n=108 F b. n=435 F B) 40-79 years	IGT	1) mean PPD 2) mean CAL	Q5 vs Q1-4: 1) OR ns 2) OR ns	5: Ag, B, PI, Sm, So
Song et al. 2016 South Korea (145) KNHANES 2008-2010	A) N=5,690 (59%M) w/PerioDz CPI=3: n=4,488 CPI=4: n=1.202 a. HOMA-IR Q4 b. HOMA-IR Q1 B) ≥30 years	HOMA-IR	PerioDz: CPI=4	Q4 vs Q1: 1) all: **OR=1.31 (1.05–1.63)** 2) non-abdominally obese: **OR=1.47 (1.16 –1.87)**	13: Ag, Al, B, De, M, O, Ph, PS, Se, Sm, So, TI, To
Timonen et al. 2011 Finland (152) Health 2000 Survey 2000-2001	A) N=2,050 (37%M) no DM a1. HOMA-IR Q5a a2. HOMA-IR Q5b b. HOMA-IR Q1 B) 30-64 years	HOMA-IR	PerioDz: # teeth with i) PPD ≥4mm ii) PPD ≥6mm	Q5 vs Q1: a1. i) RR ns; ii) RR ns a2. i) RR ns; ii) RR ns	7: Ag, Al, De, E, PI, Se, To .
Zuk et al. 2017, Canada (170)	A) N=1,383(≈50%M) no DM	1) FPG 6.1-<7.0mmol/l	PerioDz: i) no/mild:	1)&2)&3)&4): OR ns for i) & ii)	8: Ag, B, E, I, In, R,

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Canadian Health Measures Survey 2007-2009	a. n/a b. n/a B) 19-79 years	2) 6.0% ≤HbA1c ≤6.4% 3) FPG≥5.6 mmol/ or HbA1c≥6.0% 4) FPG≥5.6 mmol/ or HbA1c≥5.7%	CAL≤3mm ii) moderate/ severe: CAL≥4	Se, Sm

Bolding indicates statistical significance at p<0.05. When the lower 95% CI limit includes values shown as 1.0 or 1.00 (due to rounding), the significance is bolded if stated by the authors in the original reports, assuming the value is close to 1, but not quite equal to 1.

*Results: Risk for periodontitis incidence or prevalence from fully adjusted models

#: number; 95% CI: 95% confidence interval; ABL: alveolar bone loss; Ag: age; Al: alcohol consumption; B: body mass index/obesity (BMI); Be: betel quid chewing; BOP: bleeding on probing; C: cholesterol; Ca: caries; CAL: clinical attachment loss; CDC/AAP: Centers for Disease Control & Prevention/American Academy of Periodontology periodontitis case definitions (129) or (44); CH: cholesterol, high-density lipoprotein (HDL); CL: cholesterol, low-density lipoprotein (LDL); Co: country of origin; CPI: community periodontal index; CR: C-reactive protein (CRP); CT: cholesterol, total; D: decayed, missing, or filled teeth (DMFT); De: dental visits; Di: diet, healthy eating index; E: education; EWP: European Workshop in Periodontology (EPW) periodontitis case definitions (154); F: flossing; Fi: fruit intake; FPG: fasting plasma glucose; Fl: fluorosis; H: hypertension; HOMA: homeostatic model assessment to quantify insulin resistance (IR) and β-cell function (B), HOMA-IR = fasting insulin x fasting glucose [mmol/L]/ 22.5, HOMA-B= 20 x fasting insulin/ (fasting glucose [mmol/L] - 3.5); HR: hazard ratio; I: income, household; IGT: impaired glucose tolerance; In: insurance, health; IR: insulin resistance; IR: Insulin resistance = fasting insulin x fasting glucose; IRR: incidence rate ratio; KCIS: Keelung Community-based Integrated Screening; KNHANES: Korea National Health and Nutrition Examination Survey; M: metabolic syndrome; MONA LISA: MOnitoring NAtionaL du rISque Artériel; N (confounder): number of teeth; N: number of participants in entire study; n: number of participants in subgroup; n/a: not available; NFG: normal fasting glucose; NGT: normal glucose tolerance; NHANES: National Health and Nutrition Examination Survey (USA); NIDDK: National Institute of Diabetes, Digestive and Kidney Diseases, Phoenix, Arizona; ns: not statistically different; O: oral hygiene; OR: odds ratio; P (confounder): periodontitis, chronic (44); Pano: panoramic radiograph; PD: periodontal probing depth; PerioDz: periodontitis; Ph: physical activity; Pl: plaque (index); PreDM: prediabetes; PS: prosthetic status; PT: periodontal treatment, history; Q: quantile; R: race/ethnicity; RR: risk ratio; Se: sex/gender; Sm: smoking; So: socio-economic status; SOALS: San Juan Overweight Adults Longitudinal Study; St: study site; To: tooth brushing; T: tartar, calculus; TI: toothbrush, interproximal/other; Tr: triglyceridemia, high triglyceride levels; W: waist circumference; Y (confounder): year surveyed; y/yrs: year(s).

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Table 2. Effect of type 2 diabetes with poor glycemic control on incidence or progression of periodontitis and incident tooth loss: longitudinal studies reporting findings adjusted for potential confounders as of September 27, 2017.

Author, Year Country (Reference #) Study Population	A) Total # Subjects (M/F): a. Uncontrolled diabetes b. Well-controlled diabetes c. Normo-glycemic B) BL age (yrs)	Exposure Measure: Definition of Uncontrolled Diabetes	Outcome Measure: Periodontitis	Risk for Periodontitis* HR/IRR/OR/RR (95% CI)	#: Cofounders Controlled
Bandyopadhyay et al. 2010 USA (15) 3 years Gullah African Americans	A) N=88(19M/69F) a. 60(14M/46F) b. 28(5M/23F) c. 0 B) 34-77 (55.6)	a.HbA1c≥7.0% b.HbA1c<7.0%	Perio Dz Progression = Increase in % sites with: 1) PPD≥2mm 2) CAL≥2mm	Group a. versus b.: i) BL PPD=3mm: 1) **OR=1.98 (1.22–3.21)** 2) **OR=1.93 (1.20–3.10)** ii) BL PPD=5mm: 1) **OR=2.76 (1.52–5.01)** 2) **OR=2.64 (1.36–5.14)** iii) BL PPD=7mm: 1) **OR=3.84 (1.74–8.49)** 2) **OR=3.62 (1.45–9.05)**	3: Ag, B, Mo, Sm
Demmer et al. 2012 Germany (49) 5 years Study of Health in Pomerania	A) N=2,626 (1,234M/1,392F) a. 72 (49M/23F) b. 80(49M/31F) c. 2,280 (1,049M/1,231F) B) 20-81 a. 58(±10) b. 61(±10) c. 44(±14)	a.HbA1c≥7.0% b.HbA1c<7.0% c. no DM	I) Perio Dz Progression: 1) PPD change 2) CAL change II) Tooth loss	I) Perio Dz Progression: a. versus c.: 1) significantly greater PPD progress 2) significant, 4% greater incidence of % sites CAL≥5mm b. versus c.: 1) & 2) ns II) Tooth loss Risk for losing 1+ teeth versus c.: a.i) **RR=1.36 (1.11–1.67)**	5(6): Ag,B, (CAL), E, Se, Sm

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				a.ii) a.i adjusted for CAL@BL: RR: ns b. RR: ns Risk for losing 2+ teeth versus c.: a. **RR: ~1.6 (n/a; p<0.05)** b. RR: ns	
Morita et al. 2012 Japan (169) 5 years	A) N= 5,856 (4,511M/1,345F) a. 150(139M/11F) b. 5,706(4,372M/ 1,334F) c. n/a (incl. in b.) B) 30-69	HbA1c: a. ≥6.5% b. <6.5%	Incident Perio Dz: new CPI≥3	a. versus b.: **RR=1.17 (1.01-1.36)**	4: Ag, B, Se, Sm
Taylor et al. 1998 USA (217) Pima Indians	A) N=359 (145M/214F) a. 7(4M/3F) b. 14(3M/11F) c. 338(138M/200F) B) 15-57 a. 26 yrs (median) b. 27 c. 21	DM2 diagnosis: PG≥200mg/dL (2h-OGTT) Control: a. HbA1c >9% b. HbA1c <9% c. n/a	Incident ABL Panograms	Versus c.: a. **OR=11.4 (2.5-53.3)** b. OR: ns a. versus b.: OR: ns	7: Al, B, CD, H, N, Se, Sm

Bolding indicates statistical significance at p<0.05.
*Results: Risk for periodontitis incidence or prevalence from fully adjusted models;
#: number; 95% CI: 95% confidence interval; ABL: alveolar bone loss; Ag: age; Al: alcohol consumption; B: body mass index/obesity (BMI); BL: baseline; CD: coronary artery disease; CAL: clinical attachment loss; CPI: community periodontal index; E: education; h: hours; H: hypertension; HR: hazard ratio; IR: insulin resistance; Mo: molar; N (confounder): number of teeth; N: number of participants in entire study; n: number of participants in subgroup; n/a: not available; ns: not statistically different; OGTT: oral glucose tolerance test; OR: odds ratio; Panograms: panoramic radiographs; PPD: periodontal probing depth; Perio Dz: periodontitis; PG; plasma glucose; RR: risk ratio; Se: sex/gender; Sm: smoking; y/yrs: year(s).

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Table 3. Prevalence of various measures of hyperglycemia/diabetes and obesity assessed in two population studies in the same area of Germany conducted 10 years apart: Study of Health in Pomerania-0 1997-2001 (107,117), Study of Health in Pomerania-Trend 2008-2012 (230).

Hyperglycemia/Diabetes and Obesity mean (±SD) or % (95% CI)	Study of Health in Pomerania-0 N = 4,241 %	Study of Health in Pomerania-Trend N = 4,411 %	p-value
HbA1c, % (±SD)	5.5 (± 0.9)	5.4 (± 0.8)	**<0.001**
Self-reported diabetes (subjective diagnosis)†	8.1 (7.3-8.9)	10.5 (9.6-11.4)	**<0.001**
HbA1c ≥6.5% (objective diagnosis)	10.9 (10.0-11.9)	12.4 (11.5-13.4)	**<0.001**
HbA1c < 5.7% (normoglycemic)	70.2 (68.8–71.6)	74.3 (73.0–75.6)	**<0.001**
HbA1c 5.7-6.4% (prediabetes)	21.1 (19.8–22.3)	18.7 (17.6–19.9)	**0.006**
HbA1c ≥ 6.5% (diabetes)	8.7 (7.9–9.6)	7.0 (6.2–7.8)	**0.003**
Large waist,* %	30.7 (29.3–32.1)	36.1 (34.7–37.6)	**<0.001**
Large waist* among HbA1c ≥6.5%, %	56.6 (51.4–61.8)	72.1 (66.7–77.0)	**<0.001**
BMI ≥30.0 (obese), %	25.6 (24.3–26.9)	31.7 (30.3–33.1)	**<0.001**
BMI ≥30.0 among HbA1c ≥6.5% , %	46.6 (41.4–51.8)	61.7 (56.0–67.1)	**<0.001**
Edentulism, %	11.7 (10.7–12.7)	6.3 (5.6–7.1)	**<0.001**
Edentulous Only:	N=496	N=278	
BMI ≥ 30.0 (obese)	35.3 (31.1 39.6)	50.5 (44.5-56.6)	**<0.001**
HbA1c 5.7-6.4% (normoglycemic)	43.9 (39.5–48.4)	49.5 (43.4–55.5)	0.14
HbA1c 5.7-6.5% (prediabetes)	32.7 (28.6-37.0)	27.8 (22.6-33.6)	0.17
HbA1c ≥6.5% (diabetes)	23.4 (19.8–27.4)	22.7 (17.9–28.1)	0.82
BMI ≥30.0 among HbA1c ≥6.5%	46.2 (36.9-55.6)	66.1 (53.0-77.7)	**0.011**

† self-reported use of antidiabetic drug or self-reported doctor's diabetes diagnosis;

*Large waist: waist circumference >102cm/40inches in men or >88cm/35inches in women.

Bolding indicates statistical significance at p<0.05.

BMI: body mass index; CI: confidence interval; HbA1c: glycated hemoglobin; SD: standard deviation

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Table 4. Distribution of characteristics (potential risk factors) stratified by categories of glycemic control among dentate participants classified by periodontitis severity levels (179). Study of Health in Pomerania-0 1997-2001 (107,117) and Study of Health in Pomerania-Trend 2008-2012 (230).

Characteristic %, mean(±SD), (95% CI)*	Study of Health in Pomerania-0 N=3,410			Study of Health in Pomerania-Trend N=3,343		
	HbA1c <5.7%	HbA1c 5.7-6.4%	HbA1c ≥6.5%	HbA1c <5.7%	HbA1c 5.7-6.4%	HbA1c ≥6.5%
age (years), mean (SD)	43.5 (±14.2)	54.2 (±13.9)	60.3 (±11.8)	46.3(±14.1)	57.5 (±12.4)	60.8 (±11.4)
male sex, %	45.2	59.6	61.9	47.0	55.6	59.3
<10th grade, %	25.5	48.6	64.9	13.6	24.7	42.0
BMI≥30 (obese), %	19.8	32.9	46.5	24.2	38.2	61.1
male WC (cm),	93 (±11)	98 (±11)	104 (± 11)	94 (±12)	100 (±13)	107 (±12)
female WC (cm)	80 (±12)	88 (±13)	94 (±15)	82 (±12)	90 (±14)	99 (±15)
# teeth, mean (SD)	22.1 (± 6.0)	19.1 (± 6.7)	15.6 (± 7.1)	23.5 (±5.1)	20.5 (± 6.3)	18.8 (± 6.8)
Periodontitis:						
no/mild, %	50.4	28.2	16.3	53.6	30.9	21.6
moderate, %	32.8	42.4	46.8	32.1	44.0	47.9
severe, %	16.7	29.3	36.9	14.3	25.1	30.5
mod. vs. no/mild: PR	1	1.52 (1.28-1.81)	1.88 (1.41-2.50)	1	1.57 (1.31-1.88)	1.84 (1.35-2.50)
severe vs. no/mild: PR	1	2.04 (1.65-2.52)	2.79 (2.01-3.85)	1	2.13 (1.68-2.70)	2.79 (1.90-4.07)
CAL≥3mm, % (people)	27.6	49.3	68.8	24.0	45.1	54.5
CAL, mm, mean(±SD)	2.3 (±1.7)	3.2 (±1.8)	4.1 (±1.9)	2.2(±1.5)	3.1 (±1.7)	3.6 (±2.0)
BOP, % median (IQR)	29 (13-50)	35 (17-56)	44 (25-70)	17 (5-33)	21 (10-46)	27 (13-50)
With diabetes only (%):						
#1) self-reported,† %	1.2	5.8	63.4	2.5	14.0	66.7
#2) HbA1c ≥6.5%,‡ %	1.2	6.0	100	2.5	14.5	100
Unaware [#2) – #1)], %	n/a	0.2	36.6	n/a	0.5	33.3

† from self-reported antidiabetic drug use and/or self-reported doctor's diagnosis,

‡ including HbA1c concentration

*95% CI: 95% confidence interval, some 95% CIs omitted for clarity;

#: number; <10th grade: <10th grade education; BMI: body mass index; mod,: moderate; IQR: inter-quartile range; PR: prevalence ratio; SHIP: Study of Health in Pomerania; WC: waist circumference

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Table 5. Characteristics of study groups by diabetes status and periodontal health measures.

Periodontal Health Measure	Diabetes Mellitus	No Diabetes Mellitus
Groups with periodontal probing depth (PPD)measurements:		
Number of study groups	37	66
Number of participants	1,089	1,474
Males (%)	52.8	49.1
Mean age (years)	55.0	46.5
Mean PPD before therapy (mm)	3.2	3.9
Groups with clinical attachment level (CAL) measurements:		
Number of study groups	33	54
Number of participants	1,009	1,220
Males (%)	52.6	47.5
Mean age (years)	55.2	46.6
Mean CAL before therapy (mm)	3.2	3.8

Values represent weighted means using the sample size of each group.

PPD: periodontal probing depth; CAL: clinical attachment level/loss.

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Table 6. Studies evaluating the effect of scaling and root planing on periodontal probing depth and clinical attachment level/loss in subjects with type 2 diabetes mellitus: pre-treatment characteristics.

Author (Ref.#)	Country	Year	N	Males %	Mean Age Years	HbA1c <SRP (mean±SD) %	PPD <SRP (mean±SD) mm	CAL <SRP (mean±SD) mm
Smith et al. (208)	USA	1996	18	61.1	41.3	8.2 ± NR	2.9 ± 0.2	NR
Kiran et al. (127)	Turkey	2005	22	45.5	56.0	7.3 ± 0.7	2.3 ± 0.5	3.2 ± 1.1
Faria-Almeda et al. (76)	Spain	2006	10	80.0	56.9	7.2 ± 1.3	4.1 ± 0.3	5.8 ± 1.9
Talbert et al. (215)	USA	2006	25	48.0	49.9	8.2 ± 1.8	3.1 ± 1.5	3.0 ± 1.6
Navarro-Sanchez et al. (172)	Spain	2007	10	80.0	57.4	7.2 ± 1.3	4.1 ± 0.3	5.7 ± 1.9
O'Connell et al. (177)	Brazil	2008	15	40.0	53.5	10.7 ± 2.0	2.9 ± 0.8	NR
Al-Zahrani et al. (3)	Saudi Arabia	2009	15	46.7	52.2	8.8 ± 1.4	3.2 ± 0.7	4.7 ± 1.3
Dag et al. I (47)	Turkey	2009	15	33.3	53.1	10.0 ± 1.5	2.8 ± 0.7	4.3 ± 1.0
Dag et al. II (47)	Turkey	2009	15	46.7	52.2	6.3 ± 0.7	2.7 ± 0.5	4.3 ± 0.8
Katagiri et al. (122)	Japan	2009	32	65.6	60.3	7.2 ± 0.9	3.0 ± 0.9	NR
Santos et al. I (197)	Brazil	2009	18	44.4	52.3	9.1 ± 2.1	3.2 ± 0.5	3.8 ± 0.7
Santos et al. II (197)	Brazil	2009	18	44.4	53.0	9.2 ± 1.9	3.5 ± 0.6	4.2 ± 0.9
Correa et al. (41)	Brazil	2010	23	39.1	47.5	9.5 ± 1.7	4.2 ± 1.0	5.4 ± 1.3
Kardesler et al. I (120)	Turkey	2010	12	58.3	50.3	9.9 ± 2.4	4.1 ± 1.0	4.4 ± 1.1
Kardesler et al. II (120)	Turkey	2010	13	84.6	55.3	6.0 ± 0.5	3.7 ± 0.4	4.3 ± 0.9
Auyeung et al. I (13)	Taiwan	2012	72	62.5	56.7	7.4 ± 0.9	3.5 ± 0.6	4.2 ± 1.4
Auyeung et al. II (13)	Taiwan	2012	28	57.1	56.0	7.0 ± 0.9	2.9 ± 0.3	2.6 ± 0.6
Chen et al. I (34)	China	2012	42	54.8	59.9	7.3 ± 1.2	2.7 ± 0.7	3.6 ± 1.3
Chen et al. II (34)	China	2012	43	60.5	57.9	7.3 ± 1.6	2.6 ± 0.7	3.0 ± 1.2
Gilowski et al. (86)	Poland	2012	17	52.9	56.0	6.7 ± 1.3	2.9 ± 0.4	4.5 ± 1.3
Hungund & Panseriya (110)	India	2012	15	40.0	50.6	8.2 ± 1.6	3.6 ± 0.7	NR
Moeintaghavi et al. (164)	Iran	2012	22	59.1	50.3	8.2 ± 1.2	2.3 ± 0.7	3.1 ± 1.1
Santos et al. I (198)	Brazil	2012	17	52.9	51.9	9.4 ± 2.5	3.3 ± 0.9	3.8 ± 0.6
Santos et al. II (198)	Brazil	2012	17	41.2	53.1	8.9 ± 2.2	3.6 ± 0.6	4.2 ± 0.9
Serrano et al. (201)	Colombia	2012	17	41.2	66.6	6.6 ± 1.1	4.7 ± 0.3	4.3 ± 1.5
Engbretson et al. (68)	USA	2013	257	55.6	56.7	7.8 ± 0.7	3.3 ± 0.6	3.5 ± 0.9
Santos et al. I (199)	Brazil	2013	19	21.1	50.3	10.0 ± 2.4	3.4 ± 0.5	4.1 ± 0.9

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Santos et al. II (199)	Brazil	2013	19	31.6	53.9	10.4 ± 2.9	3.7 ± 0.8	4.4 ± 1.0
Zhang et al. (241)	China	2013	49	42.9	60.4	7.7 ± 1.2	2.5 ± 0.5	3.4 ± 1.0
Kanduluru & Naganandini (119)	India	2014	28	67.9	47.1	8.5 ± 1.5	3.1 ± 0.5	4.5 ± 1.1
Raman et al. (190)	Malaysia	2014	15	73.3	57.7	7.8 ± 1.5	2.6 ± 0.6	3.4 ± 0.8
Tsalikis et al. (223)	Greece	2014	35	51.4	57.9	6.9 ± 0.6	3.0 ± 0.7	3.8 ± 1.2
Kaur et al. I (124)	India	2015	23	43.5	52.8	6.0 ± 0.5	2.8 ± 0.4	3.3 ± 0.5
Kaur et al. II (124)	India	2015	27	44.4	50.9	10.0 ± 2.0	3.1 ± 0.5	3.6 ± 0.5
Wu et al. (239)	China	2015	23	52.2	54.1	7.4 ± 0.2	3.7 ± 0.6	3.7 ± 1.3
El-Sharkawy et al. (62)	Egypt	2016	26	65.4	51.2	8.6 ± 0.9	4.5 ± 0.7	4.9 ± 0.5
Tasdemir et al. (216)	Turkey	2016	17	17.6	51.3	7.5 ± 0.4	3.1 ± 0.5	3.7 ± 0.8

I/II: groups within the same study; CAL: clinical attachment level/loss; HbA1c: glycated hemoglobin; N: number of participants; NR: not reported; PPD: periodontal probing depth; Ref. #: reference number; SD: standard deviation; SRP: scaling and root planing

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Table 7. Studies evaluating the effect of scaling and root planing on periodontal probing depth and clinical attachment level/loss in subjects without diabetes: pre-treatment characteristics.

Author (Ref.#)	Country	Year	N	Males %	Mean Age Years	PPD <SRP (mean±SD) mm	CAL <SRP (mean±SD) mm
Haffajee et al. (101)	USA	1997	57	50.9	47.1	3.3 ± 0.1	2.9 ± 0.2
Feres et al. (78)	USA	1999	10	60.0	54.0	3.1 ± 0.4	3.2 ± 0.9
Winkel et al. (236)	Netherlands	1999	11	36.4	39.0	3.8 ± 0.5	NR
Eren et al. I (70)	Turkey	2002	50	68.0	47.1	4.8 ± 0.6	NR
Eren et al. II(70)	Turkey	2002	50	70.0	45.8	4.8 ± 0.5	NR
VanSteijn et al. (227)	Netherlands	2002	16	37.5	43.0	3.7 ± 0.9	4.1 ± 1.9
Apatzidou & Kinane I (10)	UK	2004	20	65.0	42.0	4.4 ± 0.7	5.0 ± 0.9
Apatzidou & Kinane II (10)	UK	2004	20	50.0	48.0	4.4 ± 0.7	5.1 ± 1.0
Carvalho et al. (29)	Brazil	2004	10	30.0	41.0	4.0 ± 0.7	4.5 ± 0.9
Emingil et al. (65)	Turkey	2004	10	60.0	47.8	4.0 ± 0.2	4.7 ± 0.3
Colombo et al. (40)	Brazil	2005	25	48.0	43.0	3.4 ± 0.8	3.7 ± 1.2
Mascarenhas (149)	USA	2005	15	53.3	45.3	3.5 ± 0.7	3.9 ± 1.0
Preshaw et al. I (188)	UK	2005	10	50.0	42.8	3.3 ± 0.6	NR
Preshaw et al. II (188)	UK	2005	10	40.0	42.8	4.0 ± 0.7	NR
Gorska & Nedzi-Gora (89)	Poland	2006	33	45.5	44.0	2.3 ± 0.6	2.9 ± 1.5
Gomi et al. (87)	Japan	2007	17	47.1	51.0	4.1 ± 0.7	7.2 ± 1.4
Haffajee et al. (100)	US	2007	23	60.9	43.0	2.9 ± 0.4	3.0 ± 0.6
Yoshie et al. (240)	Japan	2007	49	49.0	55.1	3.2 ± 0.1	3.9 ± 0.2
Emingi et al. I (63)	Turkey	2008	12	58.3	47.8	3.9 ± 0.5	4.7 ± 0.7
Guentsch et al. (94)	Germany	2008	21	47.6	59.0	5.0 ± 0.4	5.2 ± 0.6
Matarazzo et al. (150)	Brazil	2008	15	46.7	40.5	3.9 ± 0.6	4.7 ± 1.2
Cionca et al. (38)	Switzerland	2009	24	41.7	50.5	4.4 ± 0.4	NR
Dağ et al. (47)	Turkey	2009	15	53.3	49.5	2.6 ± 0.4	4.3 ± 0.6
Feres et al. (77)	Brazil	2009	20	45.0	39.6	3.7 ± 0.7	4.1 ± 0.9
Bokhari et al. (21)	Pakistan	2009	11	63.6	43.7	2.0 ± 0.6	NR
Ioannou et al. I (114)	Greece	2009	16	50.0	49.6	3.9 ± 0.2	5.4 ± 0.4
Ioannou et al. II (114)	Greece	2009	17	35.3	50.5	3.5 ± 0.2	4.5 ± 0.4
Swierkot et al. I (214)	Germany	2009	7	14.3	48.0	3.6 ± 0.9	4.2 ± 1.0

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Swierkot et al. t II (214)	Germany	2009	9	22.2	50.0	3.6 ± 0.9	4.2 ± 0.7
Swierkot et al. III (214)	Germany	2009	9	22.2	39.0	3.2 ± 0.6	3.7 ± 0.9
Oteo (178)	Spain	2010	13	61.5	47.1	2.8 ± 0.1	3.6 ± 0.3
Shimada et al. (202)	Japan	2010	33	24.2	55.1	3.7 ± 0.7	4.3 ± 0.9
Emingil (64)	Turkey	2011	23	65.2	47.7	4.2 ± 0.8	5.2 ± 1.2
Winkel et al. (235)	Netherlands	2001	26	38.5	40.0	4.4 ± 0.5	4.0 ± 1.3
Hungund & Panseriya (110)	India	2012	15	60.0	40.7	3.0 ± 0.6	NR
Kruck et al. (132)	Germany	2012	17	52.9	51.0	3.0 ± 0.4	3.3 ± 0.7
Feres et al. (79)	Brazil	2013	40	30.0	45.8	3.8 ± 0.7	4.3 ± 1.0
Mombelli et al. I (166)	Switzerland	2013	19	42.1	46.9	4.5 ± 1.8	NR
Mombelli et al. II (166)	Switzerland	2013	19	52.6	49.9	4.5 ± 1.4	NR
Preus et al. I (189)	Norway	2013	45	35.6	55.1	3.0 ± 0.6	1.7 ± 1.0
Preus et al. II (189)	Norway	2013	47	48.9	54.9	3.2 ± 0.6	1.9 ± 1.1
Shirmohammadi et al. I (203)	Iran	2013	20	50.0	47.7	4.2 ± 0.7	4.2 ± 0.7
Shirmohammadi et al. II (203)	Iran	2013	20	55.0	43.0	4.2 ± 0.6	4.2 ± 0.6
Teughels et al. (220)	Turkey	2013	15	53.3	45.7	4.3 ± 0.5	NR
Ardais et al. I (12)	Brazil	2014	14	35.7	47.6	3.3 ± 0.4	3.0 ± 1.0
Ardais et al. II (12)	Brazil	2014	11	36.4	47.0	3.5 ± 0.5	4.9 ± 1.5
Perayil et al. (180)	India	2014	30	53.3	45.3	6.3 ± 0.4	6.3 ± 0.2
Pradeep et al. (187)	India	2014	32	50.0	36.8	6.5 ± 1.2	7.6 ± 1.2
Al Habashneh et al. (4)	Jordan	2015	21	33.3	39.0	2.4 ± 0.4	1.7 ± 1.2
Fonseca et al. I (80)	Brazil	2015	15	40.0	44.6	2.3 ± 0.6	2.5 ± 1.4
Fonseca et al. II (80)	Brazil	2015	13	38.5	44.6	2.2 ± 0.6	2.4 ± 1.0
Goncalves et al. I (88)	Brazil	2015	20	50.0	48.5	3.4 ± 0.6	4.4 ± 0.8
Goncalves et al. II (88)	Brazil	2015	20	55.0	50.0	3.6 ± 0.6	4.9 ± 1.0
Graziani et al. I (90)	Italy	2015	19	47.4	48.0	3.2 ± 0.5	3.9 ± 0.8
Graziani et al. II (90)	Italy	2015	19	47.4	46.0	3.6 ± 0.6	4.4 ± 0.8
Laleman et al. (133)	Turkey	2015	24	58.3	47.0	4.6 ± 0.5	5.4 ± 0.5
Mombelli et al. (165)	Switzerland	2015	40	55.0	48.9	3.6 ± 0.8	4.1 ± 1.2
Pradeep et al. (186)	India	2015	32	46.9	35.9	6.0 ± 0.9	6.6 ± 0.9
Tekce et al. (218)	Turkey	2015	20	50.0	41.4	5.4 ± 0.7	NR
Azad et al. (14)	Germany	2016	23	56.5	50.9	3.3 ± 0.3	3.4 ± 0.3
Bizzarro et al. (20)	Netherlands	2016	29	72.4	48.2	3.9 ± 0.6	4.4 ± 0.8

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Cosgarea et al. (42)	Romania	2016	30	36.7	42.5	5.5 ± 0.6	5.9 ± 1.2
Martande et al. (146)	India	2016	35	60.0	33.3	6.7 ± 1.4	7.6 ± 1.4
Morales et al. (168)	Chile	2016	14	50.0	46.9	2.5 ± 0.3	4.9 ± 1.3
Sangwan et al. (195)	India	2016	35	48.6	43.0	2.9 ± 0.5	3.5 ± 0.7
Tasdemir et al. (216)	Turkey	2016	14	35.7	49.2	2.9 ± 0.3	3.6 ± 0.5

I/II: groups within the same study; CAL: clinical attachment level/loss; NR: not reported; PPD: periodontal probing depth; SD: standard deviation; SRP: scaling and root planing

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Table 8. Coefficients from meta-regression analyses* of the associations between baseline glycemic control and periodontal probing depth before and 3 months after scaling and root planing.

Model 1: Adjusted for mean age and proportion of males

	Mean PPD at baseline mm		Mean PPD at 3 months after SRP, mm		Reduction of mean PPD 3 months after SRP, mm	
	B (95%CI)	p-value	B (95% CI)	p-value	B (95% CI)	p-value
Baseline HbA1c, %	0.14 (-0.06; 0.34)	0.16	0.06 (-0.09; 0.21)	0.43	0.09 (-0.02; 0.20)	0.09
Mean age, years	0.02 (-0.03; 0.07)	0.52	0.01 (-0.03; 0.04)	0.67	0.01 (-0.02; 0.04)	0.49
Proportion of males, 10%	0.09 (-0.06; 0.24)	0.24	0.04 (-0.07; 0.16)	0.43	0.05 (-0.03; 0.13)	0.19

Model 2: Model 1 with additional adjustment for mean PPD at baseline

	Mean PPD 3 months after SRP, mm		Reduction of mean PPD 3 months after SRP, mm	
	B (95% CI)	p-value	B (95% CI)	p-value
Baseline HbA1c, %	-0.03 (-0.12; 0.05)	0.45	0.04 (-0.05; 0.13)	0.34
Mean PPD at baseline, mm	**0.64 (0.49; 0.79)**	**<0.001**	**0.34 (0.19; 0.50)**	**<0.001**
Mean age, years	-0.002 (-0.02; 0.02)	0.84	0.004 (-0.02; 0.03)	0.69
Proportion of males, 10%	-0.01 (-0.08; 0.05)	0.68	0.02 (-0.04; 0.09)	0.51

*using aggregate-level data based on 37 groups with 1,089 subjects. The analytic weight for each group is proportional to the precision of the respective estimate.
Bolding indicates statistical significance at p<0.05.
CI: confidence interval; B; coefficient; HbA1c: glycated hemoglobin; PPD; periodontal probing depth; SRP: scaling and root planing

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Table 9. Coefficients from meta-regression analyses* of the associations between baseline glycemic control and clinical attachment level/loss before and 3 months after scaling and root planing.

Model 1: Adjustment for mean age and proportion of males

	Mean CAL at baseline, mm		Mean CAL 3 months after SRP, mm		Reduction of mean CAL 3 months after SRP, mm	
	B (95%CI)	p-value	B (95%CI)	p-value	B (95%CI)	p-value
Baseline HbA1c, %	0.17 (-0.10; 0.44)	0.21	0.16 (-0.09; 0.41)	0.20	0.01 (-0.11; 0.13)	0.88
Mean age, years	-0.01 (-0.09;0.07)	0.82	0.01 (-0.07; 0.08)	0.88	-0.02 (-0.05; 0.02)	0.30
Proportion of males, 10%	0.16 (-0.03; 0.36)	0.09	**0.18 (0.001; 0.36)**	**0.04**	-0.01 (-0.10; 0.07)	0.73

Model 2: Model 1 with additional adjustment for mean CAL at baseline

	Mean CAL 3 months after SRP, mm		Reduction of mean CAL 3 months after SRP, mm	
	B (95%CI)	p-value	B (95%CI)	p-value
Baseline HbA1c, %	0.02 (-0.10; 0.13)	0.75	-0.02 (-0.13; 0.10)	0.75
Mean baseline CAL, mm	**0.84 (0.67; 1.00)**	**<0.001**	0.16 (-0.001; 0.32)	0.05
Mean age, years	0.02 (-0.02; 0.05)	0.35	-0.02 (-0.05; 0.02)	0.34
Proportion of males, 10%	0.04 (-0.05; 0.12)	0.35	-0.04 (-0.12; 0.05)	0.35

*using aggregate-level data based on 33 groups with 1,009 subjects. The analytic weight for each group is proportional to the precision of the respective estimate.
Bolding indicates statistical significance at p<0.05.
CI: confidence interval; B; coefficient; CAL: clinical attachment level/loss; HbA1c: glycated hemoglobin; SRP: scaling and root planing

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Table 10. Diabetes as a risk factor for tooth loss during periodontal maintenance in retrospective studies using multivariate analyses published from 1996.

Author	Publication Year	N	Study Duration (years)	Diabetes	Diabetes Efffect	Smoking
Carnevale et al. (28)	2007	300	7.8	NR	NR	reported
Chambrone & Chambrone (31)	2006	120	17.4	excluded	NR	reported
Costa et al. (44)	2013	212	5	reported	sig	reported
Eickholz et al. (58)	2008	100	10.5	reported	ns	reported
Faggion et al. (73)	2007	198	11.8	reported	sig	NR
Fardal et al. (75)	2004	100	9.8	NR	NR	reported
Jansson & Lagervall (115)	2008	60	16.2	NR	NR	reported
König et al. (130)	2002	146	10.5	NR	NR	reported
Martinez-Canut (147)	2015	500	20	NR	NR	reported
Matthews et al. (151)	2001	335	16.1	NR	NR	reported
Matuliene et al. (153)	2008	199	11	reported	ns	reported
McGuire & Nunn (155)	1996	100	9.9	reported	ns	reported
McLeod et al. (156)	1998	114	12.5	NR	NR	NR
Miyamato et al. (163)	2006	505	≥10.0	NR	NR	reported
Muzzi et al. (170)	2006	60	10.0	excluded	NR	excluded
Ng et al. (173)	2011	273	10.7	reported	ns	reported
Tsami et al. (224)	2009	280	10.8	NR	NR	reported

N: number of periodontal patients; N/R: not reported; ns: not statistically significant; sig: statistically significant

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Fig. 1

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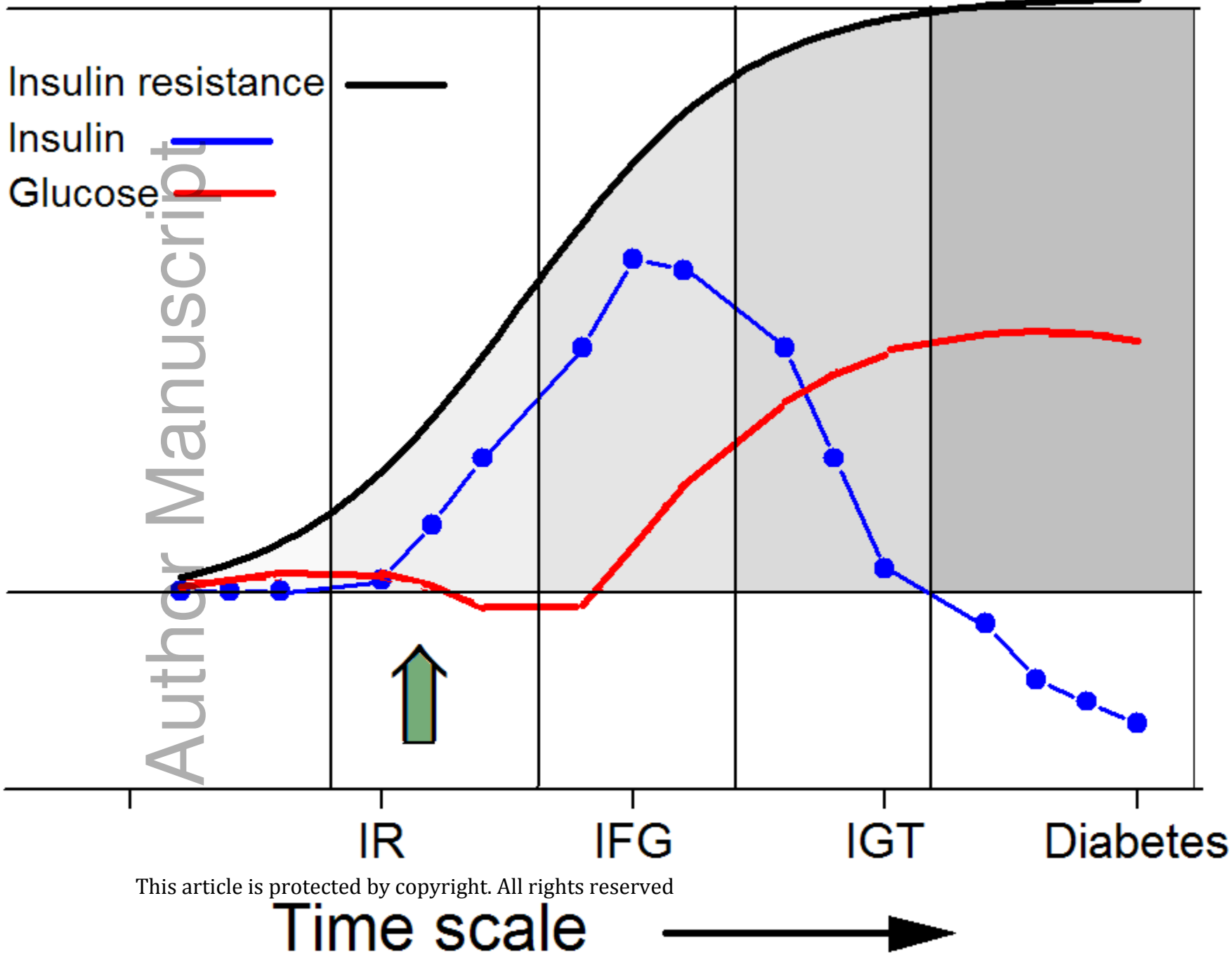

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Fig. 2

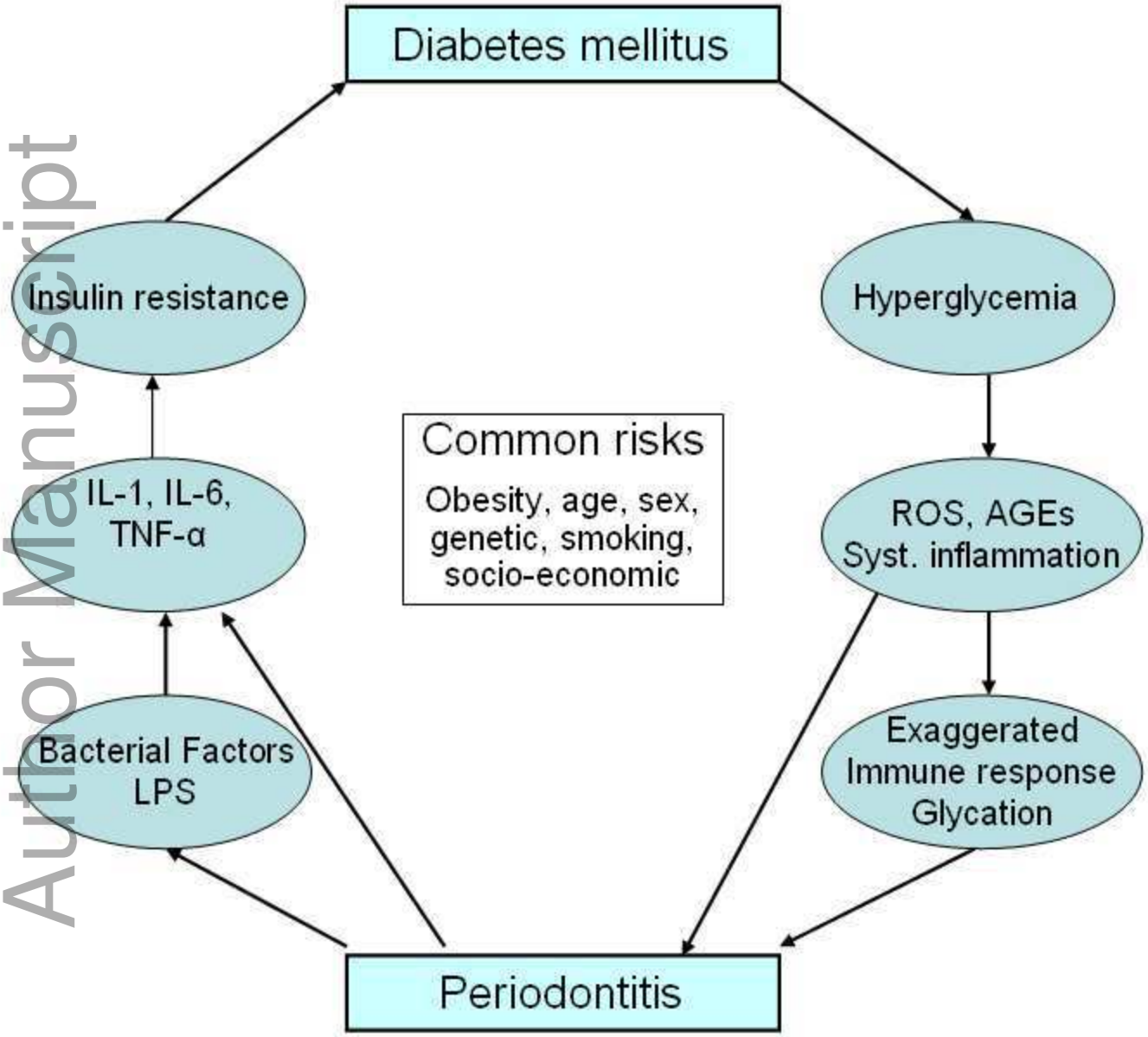

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Fig. 3

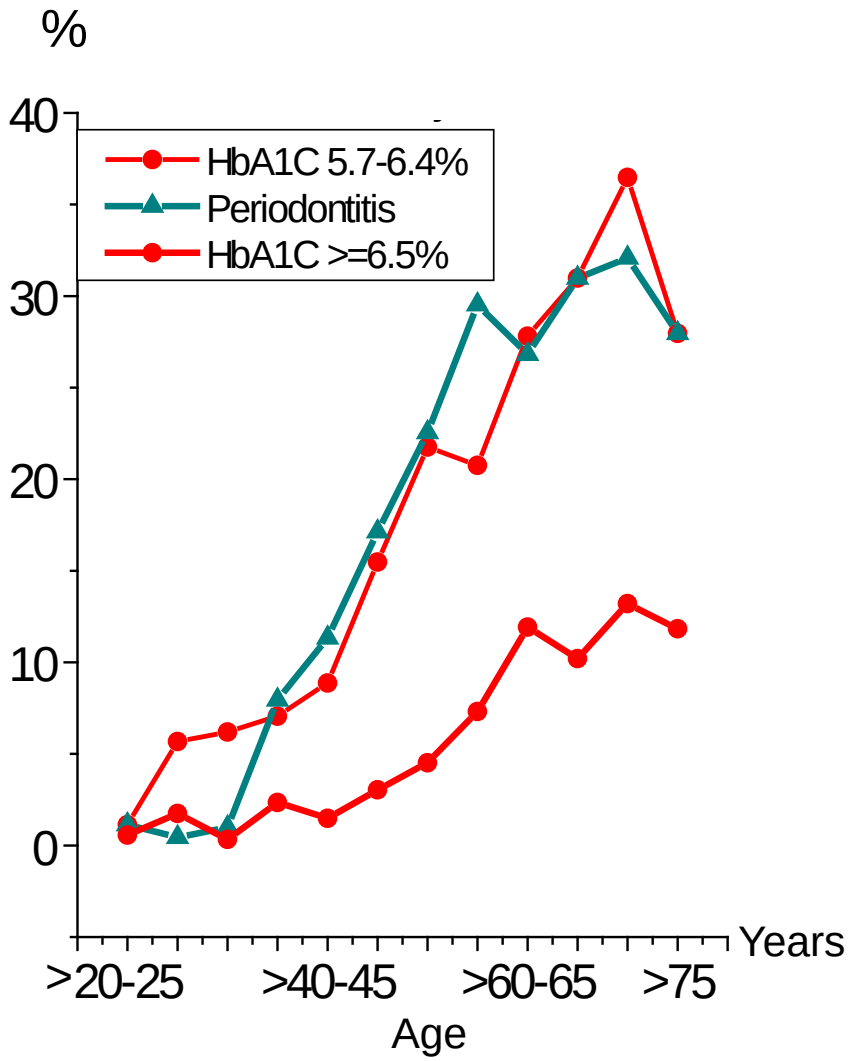

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Fig. 4

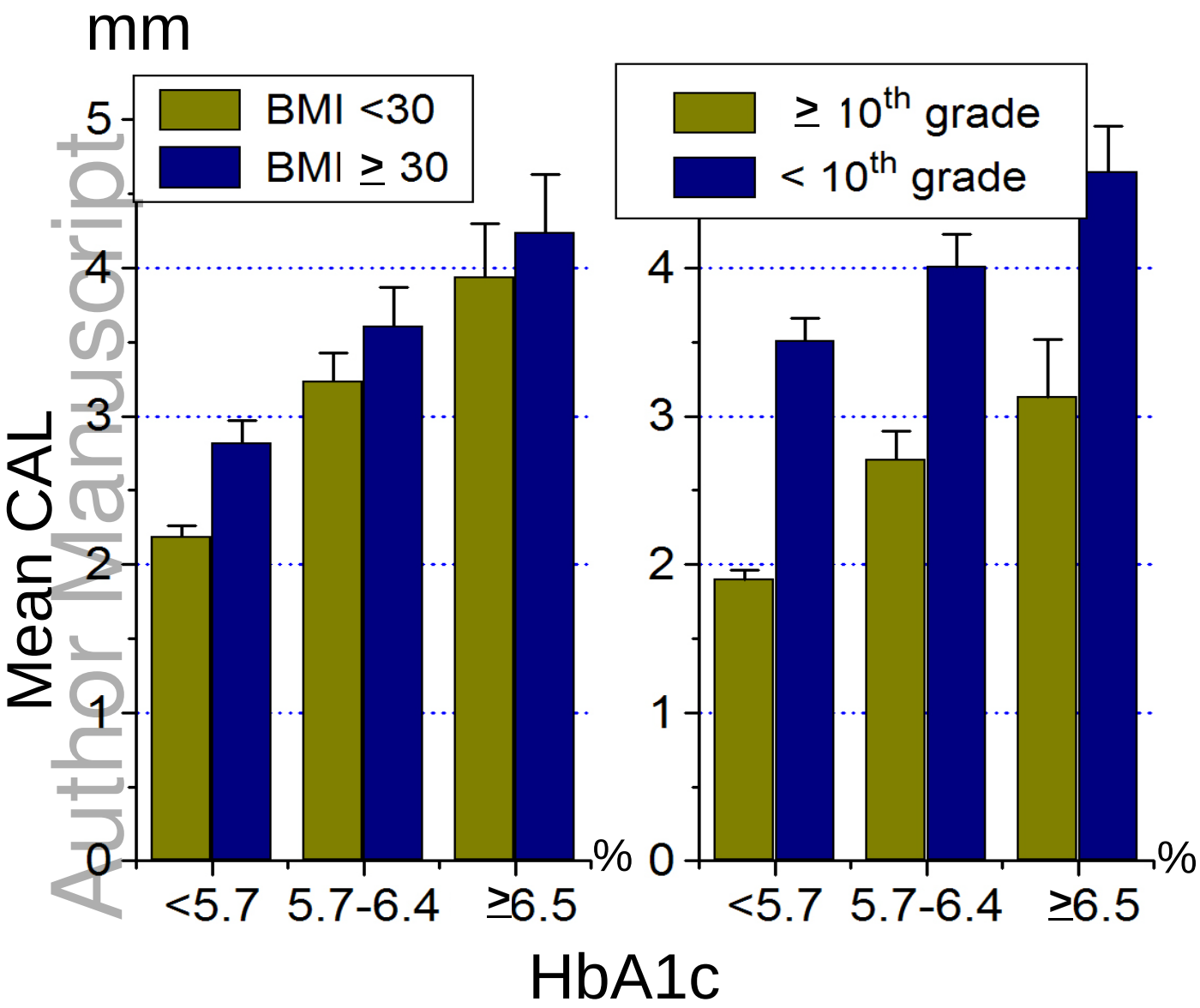

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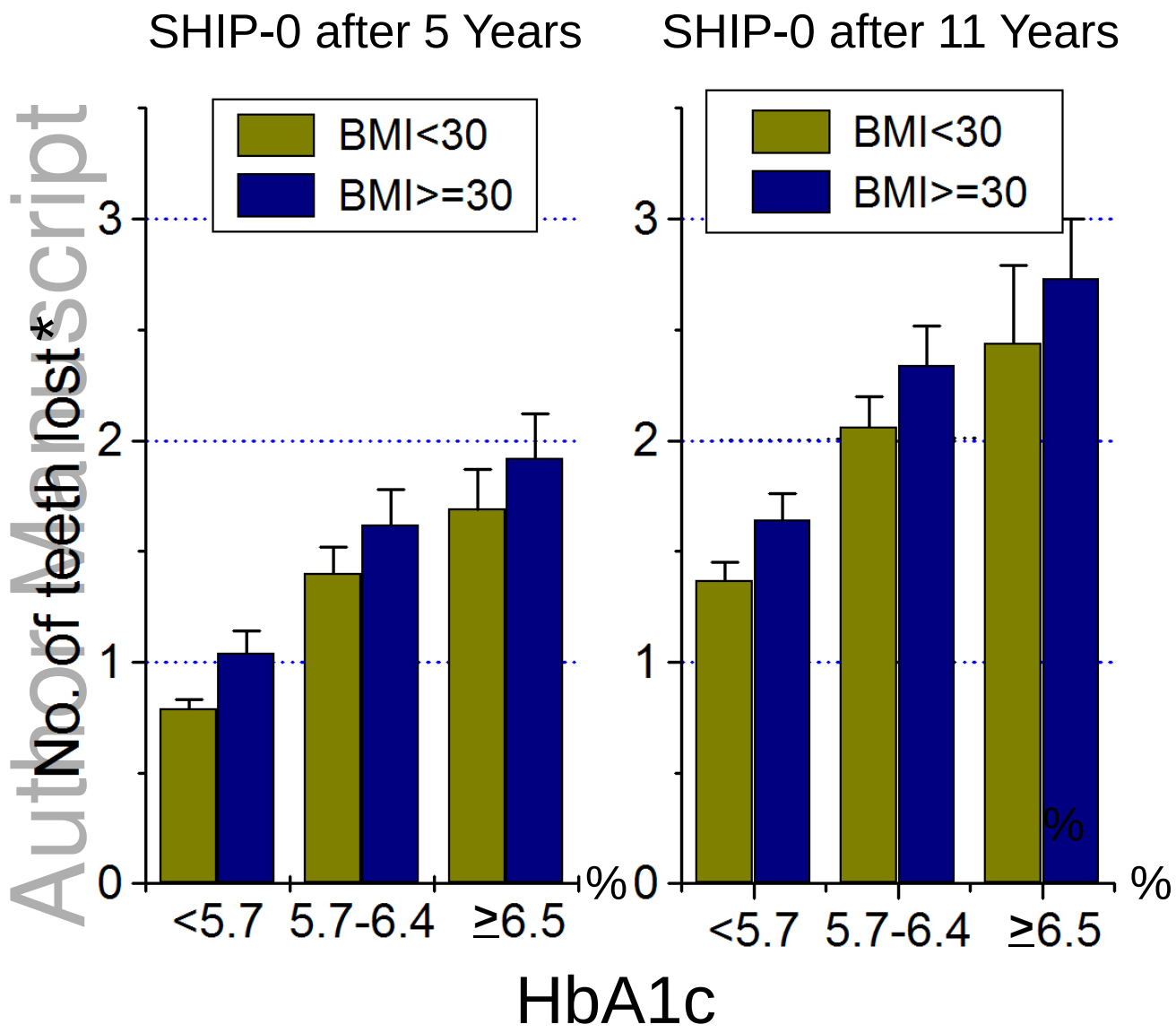
Fig. 5



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*zero-inflated Poisson regression

Fig. 6

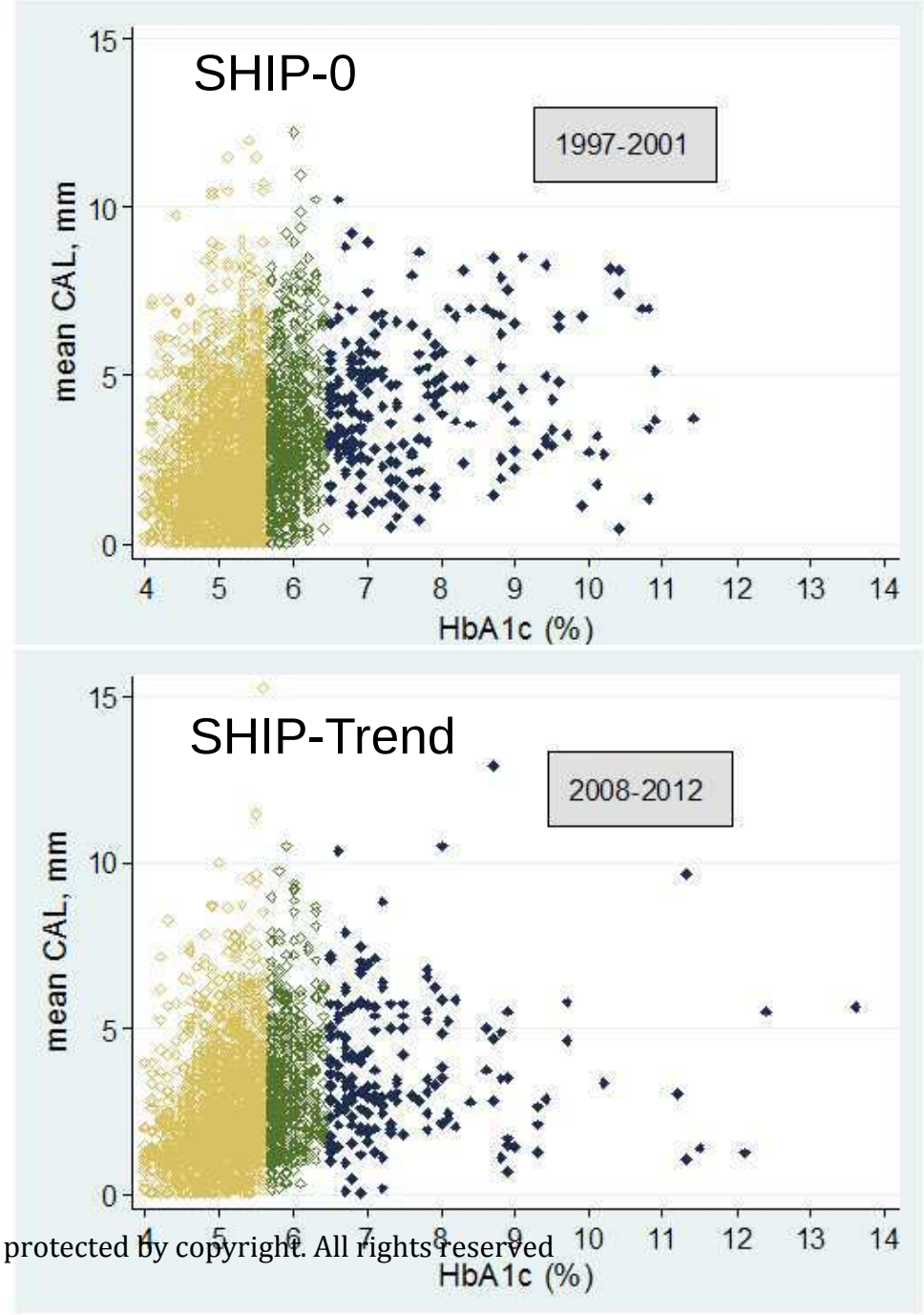

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Fig. 7

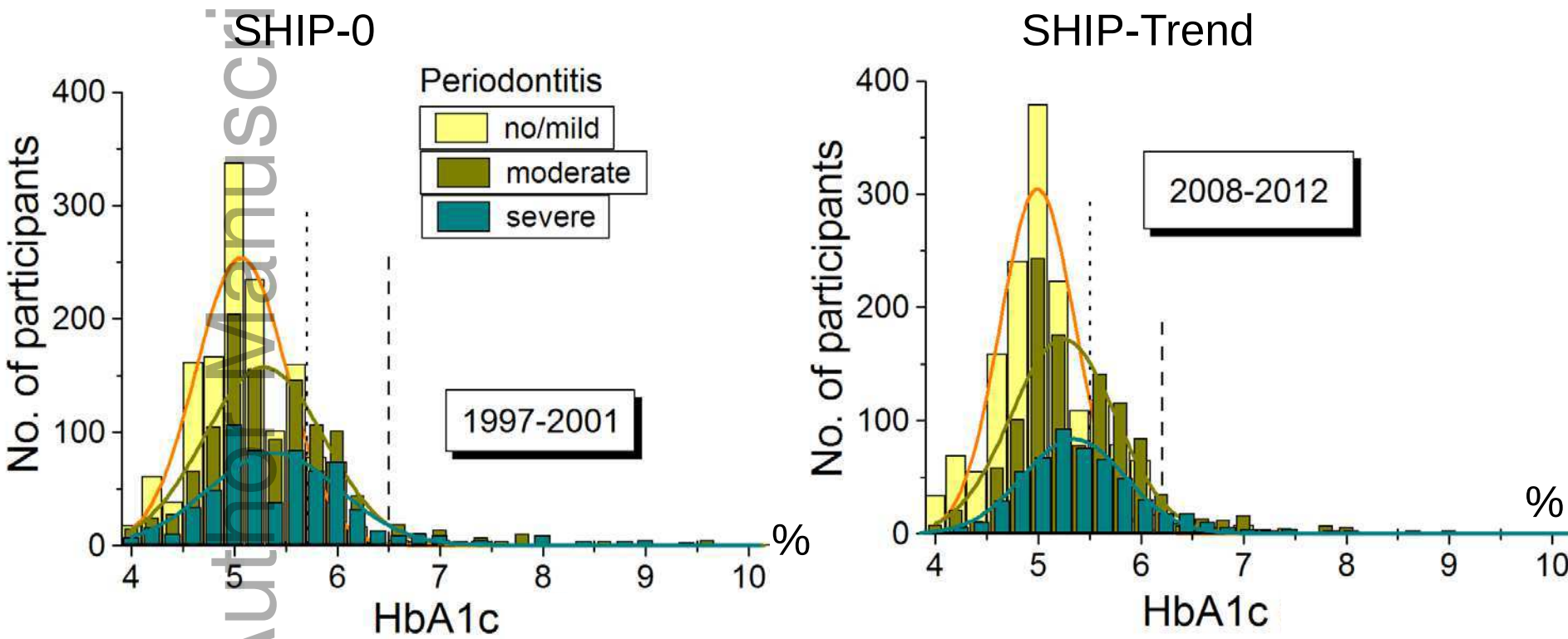

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Fig. 8

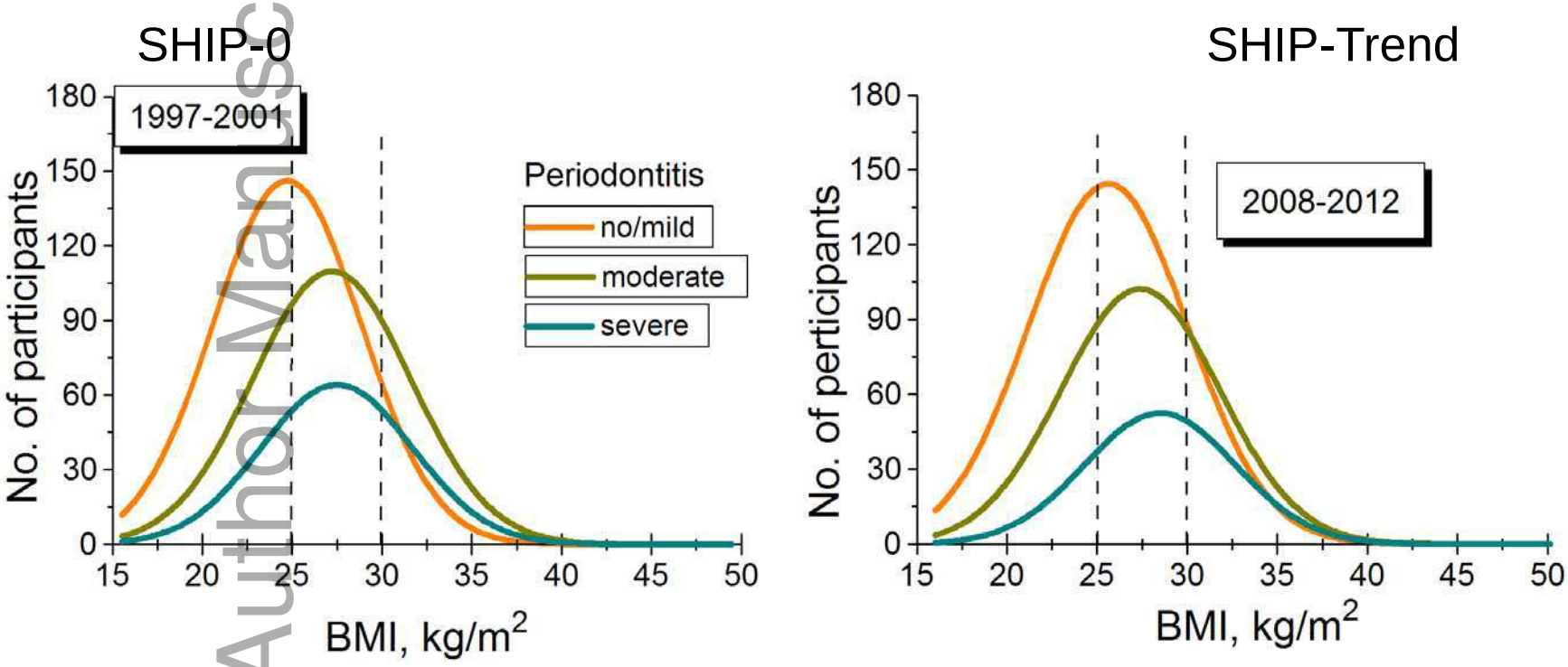

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Figure 9

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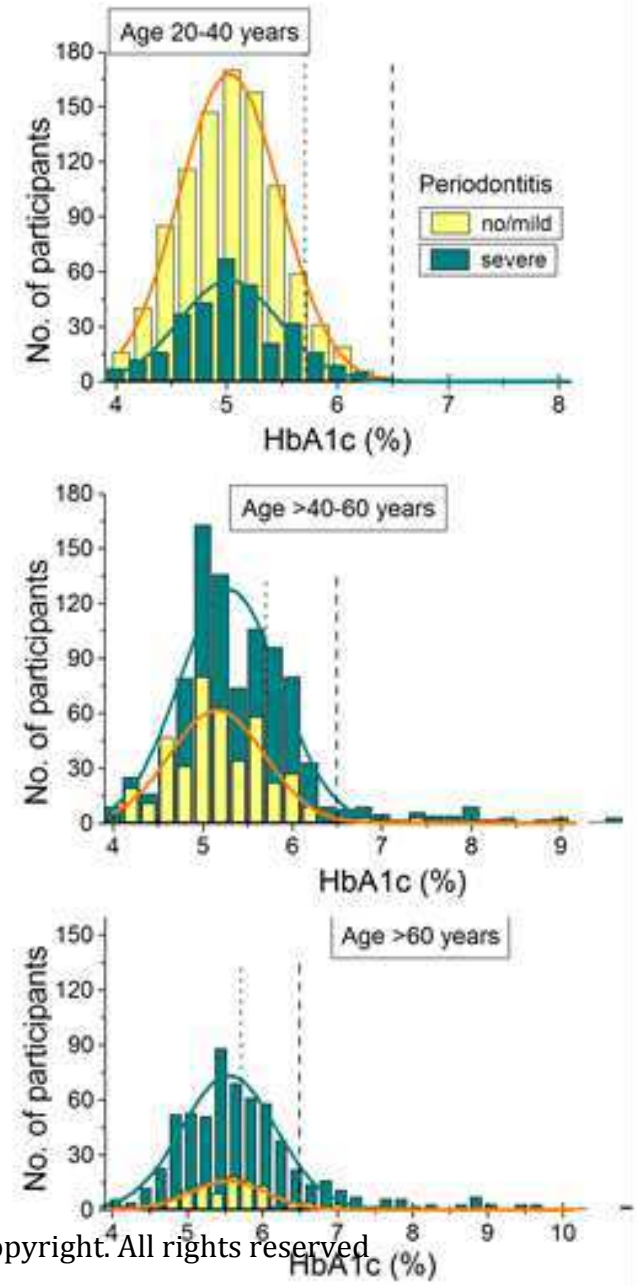

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Figure 10

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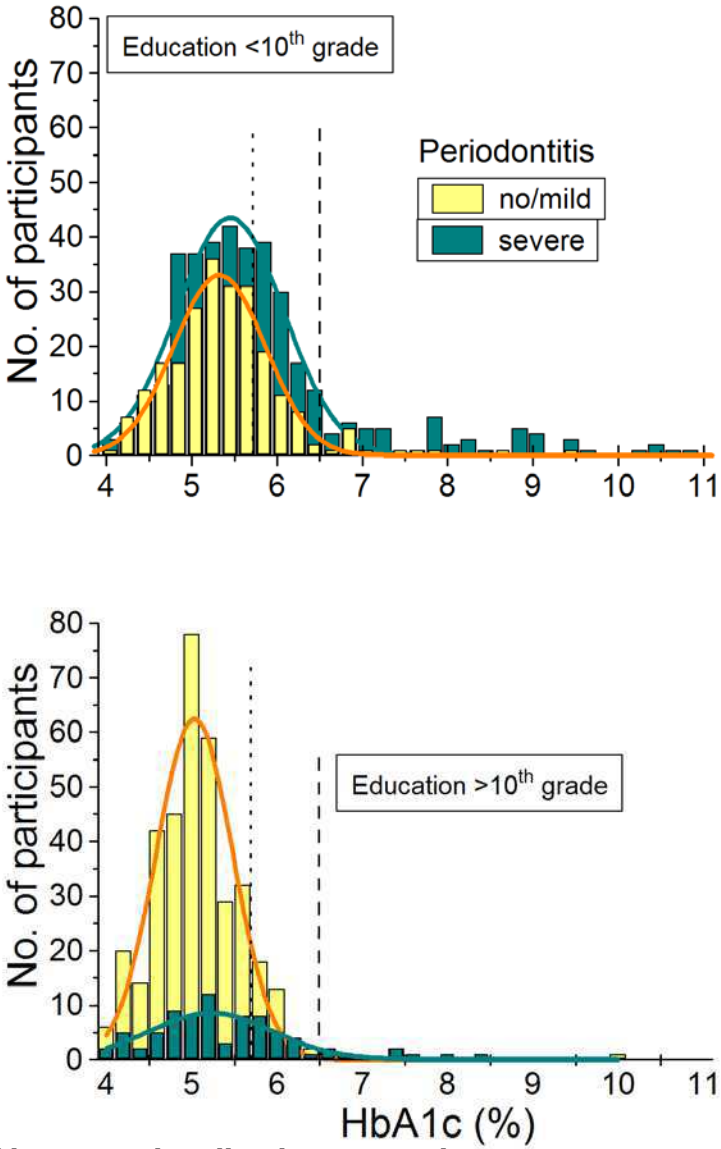

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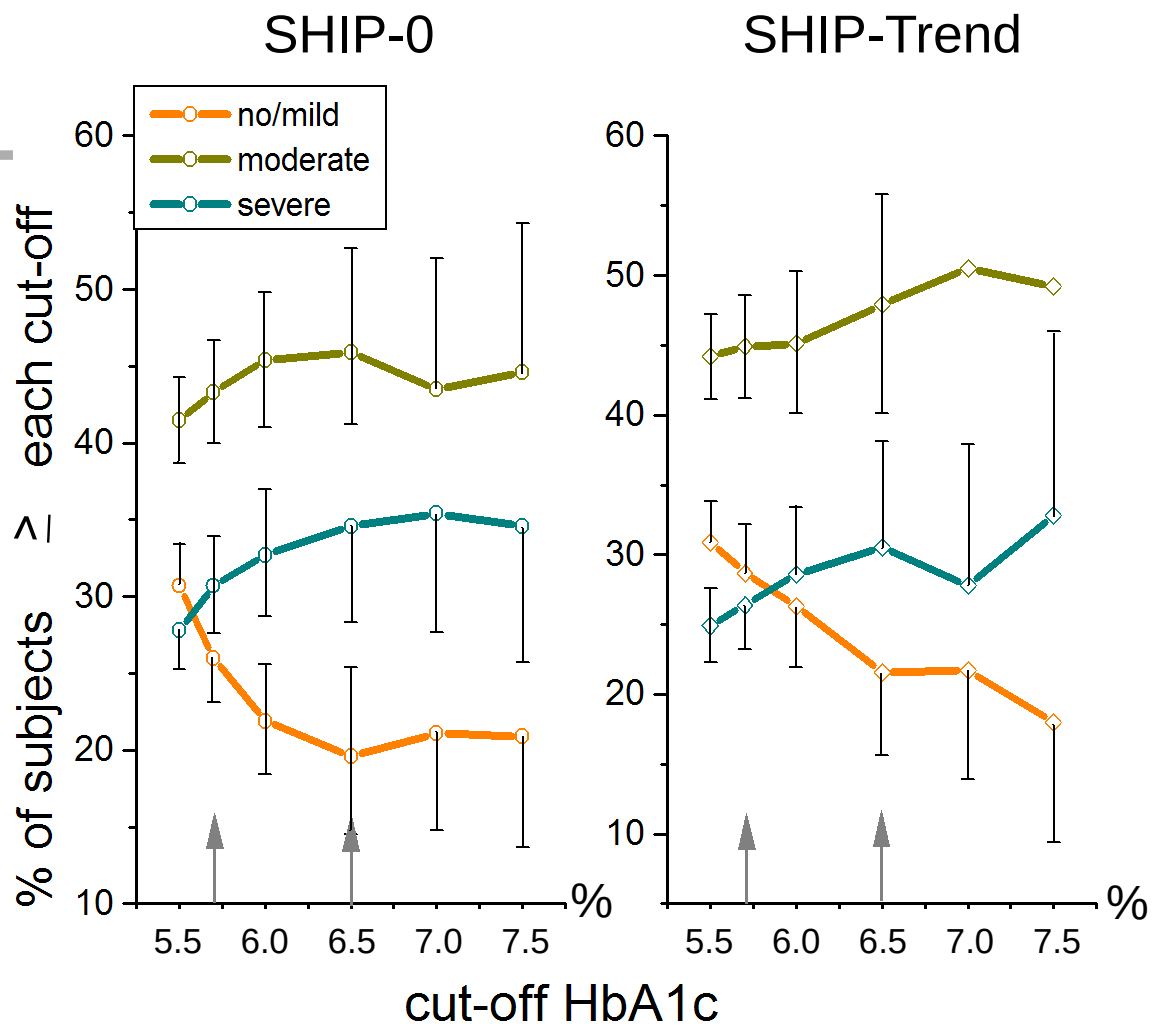
Fig. 11



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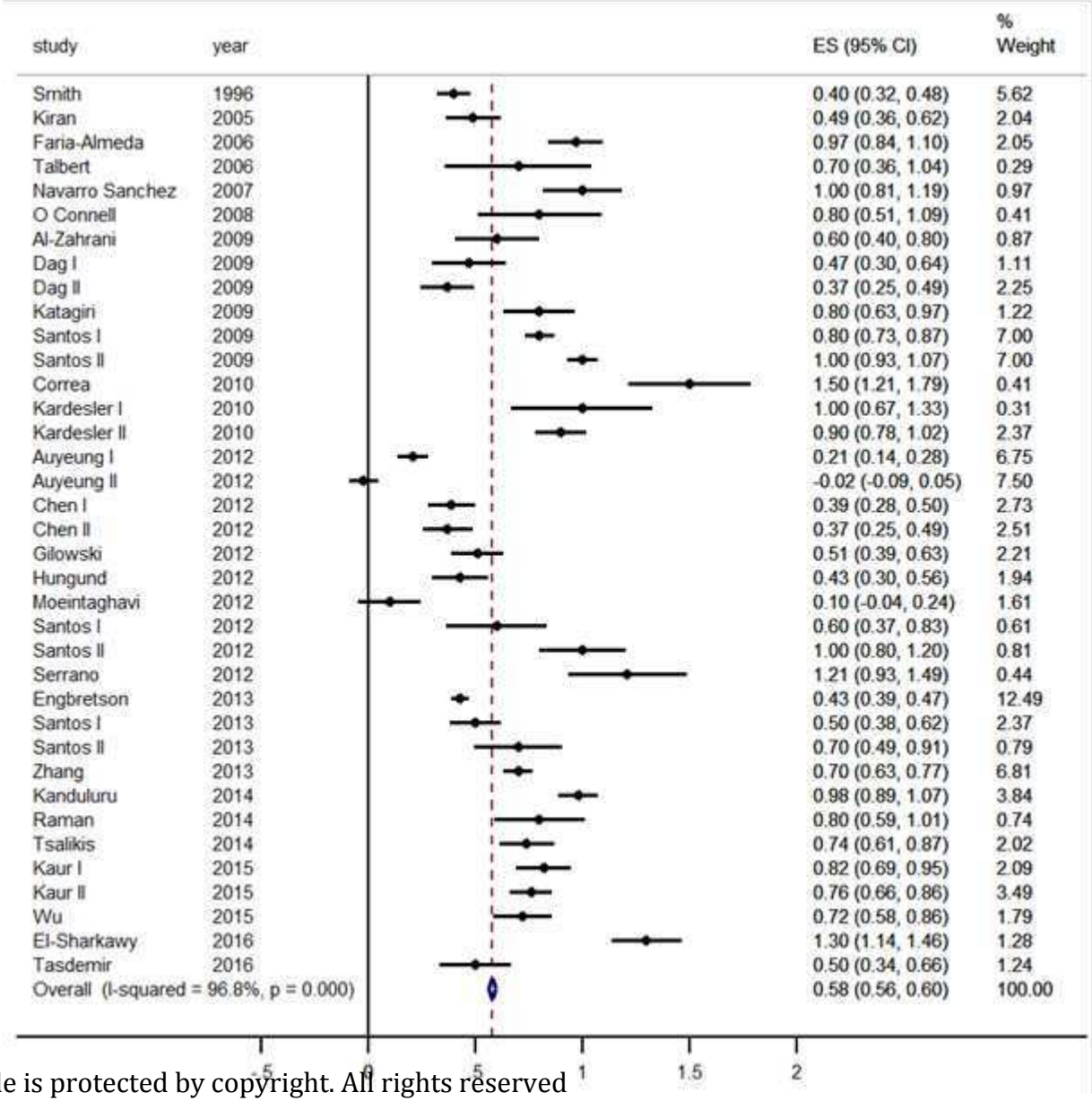

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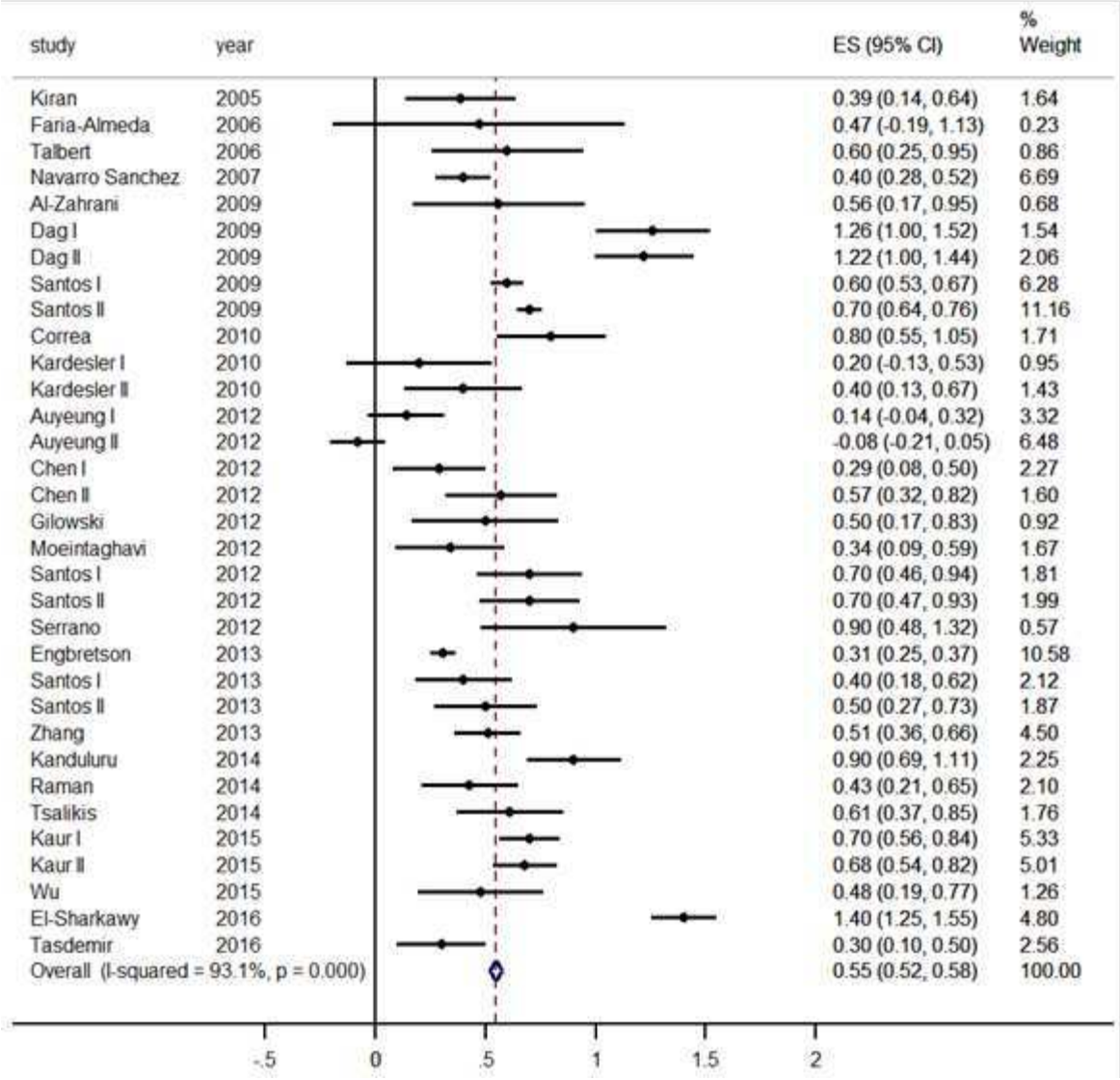

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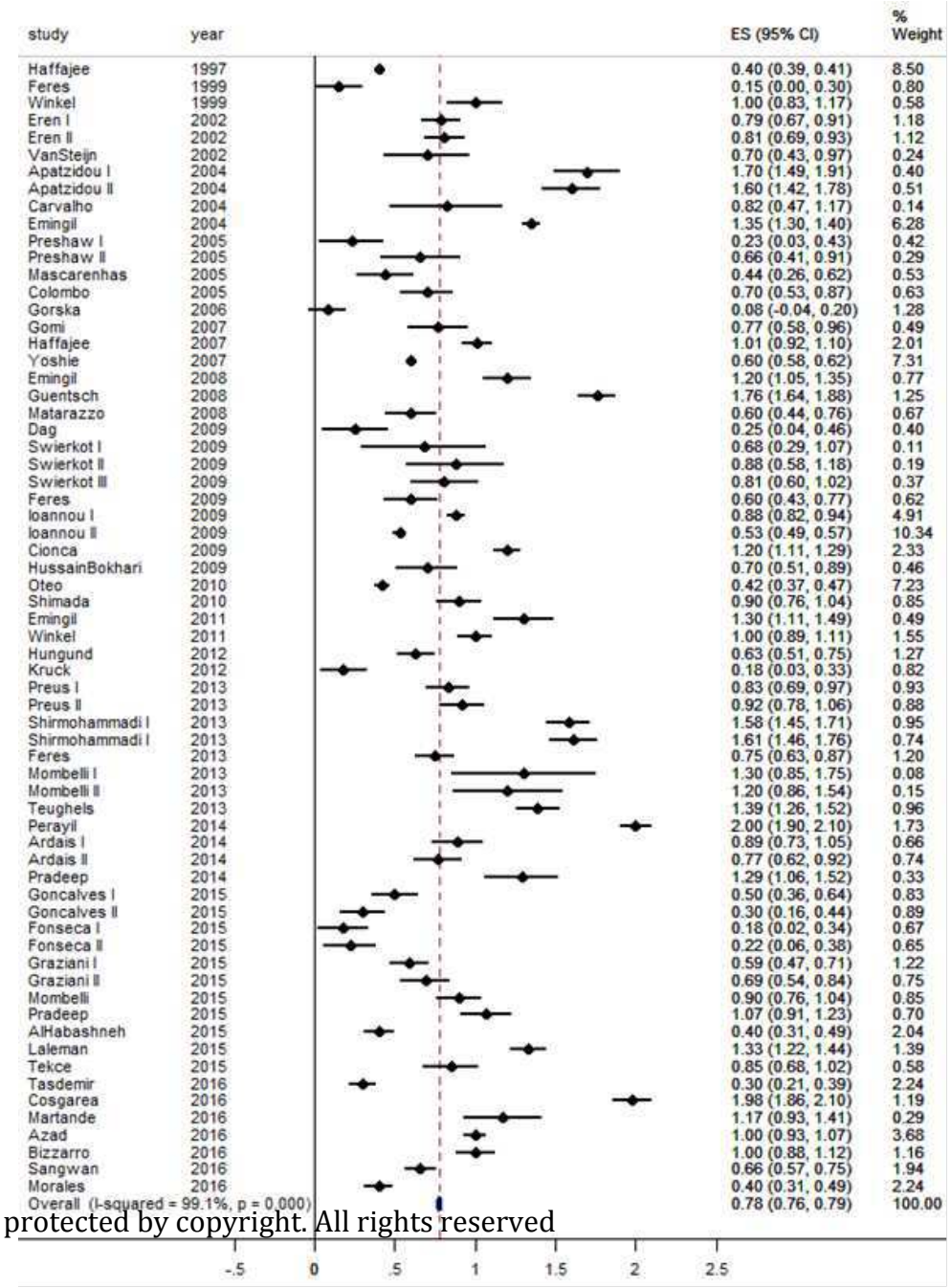

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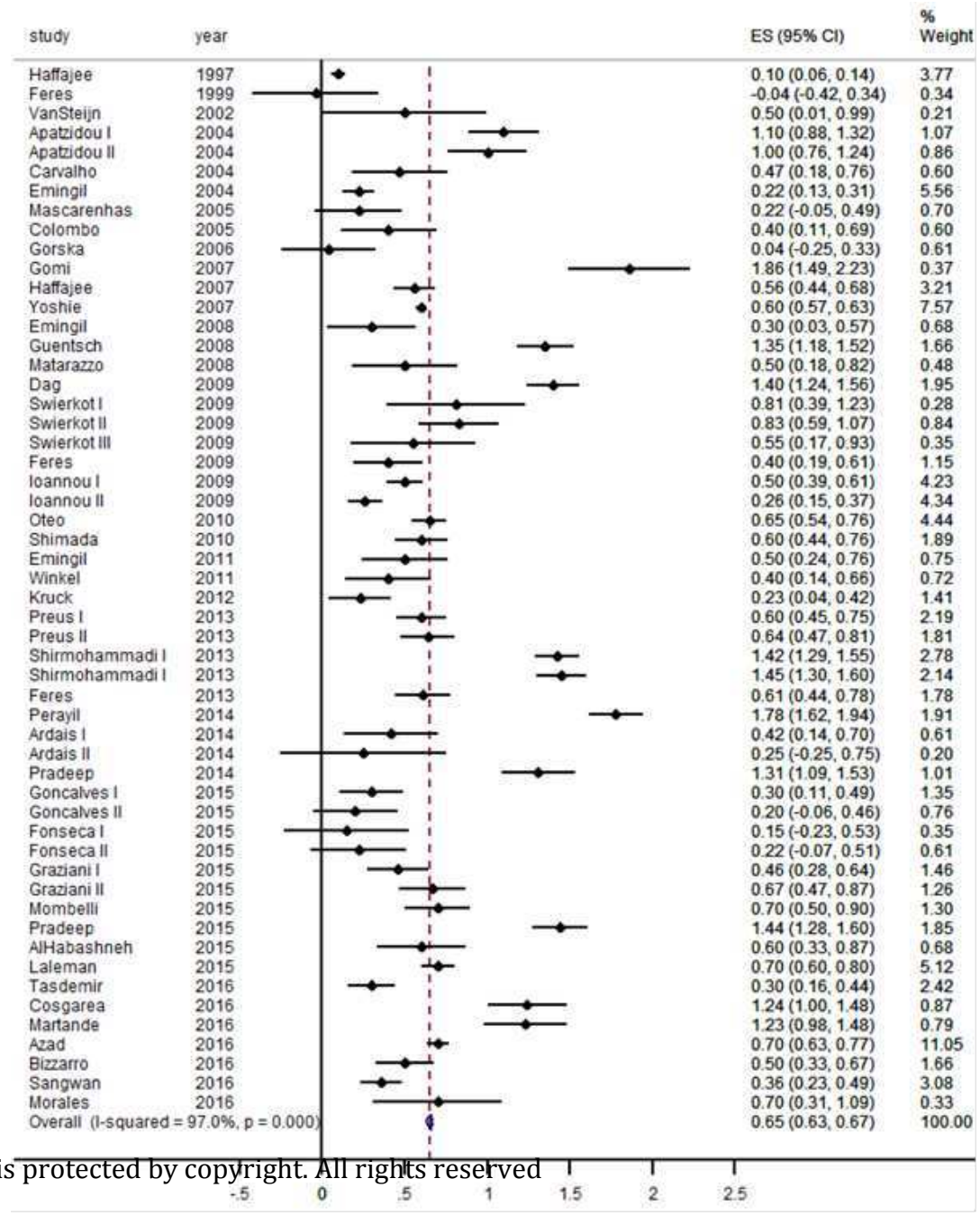

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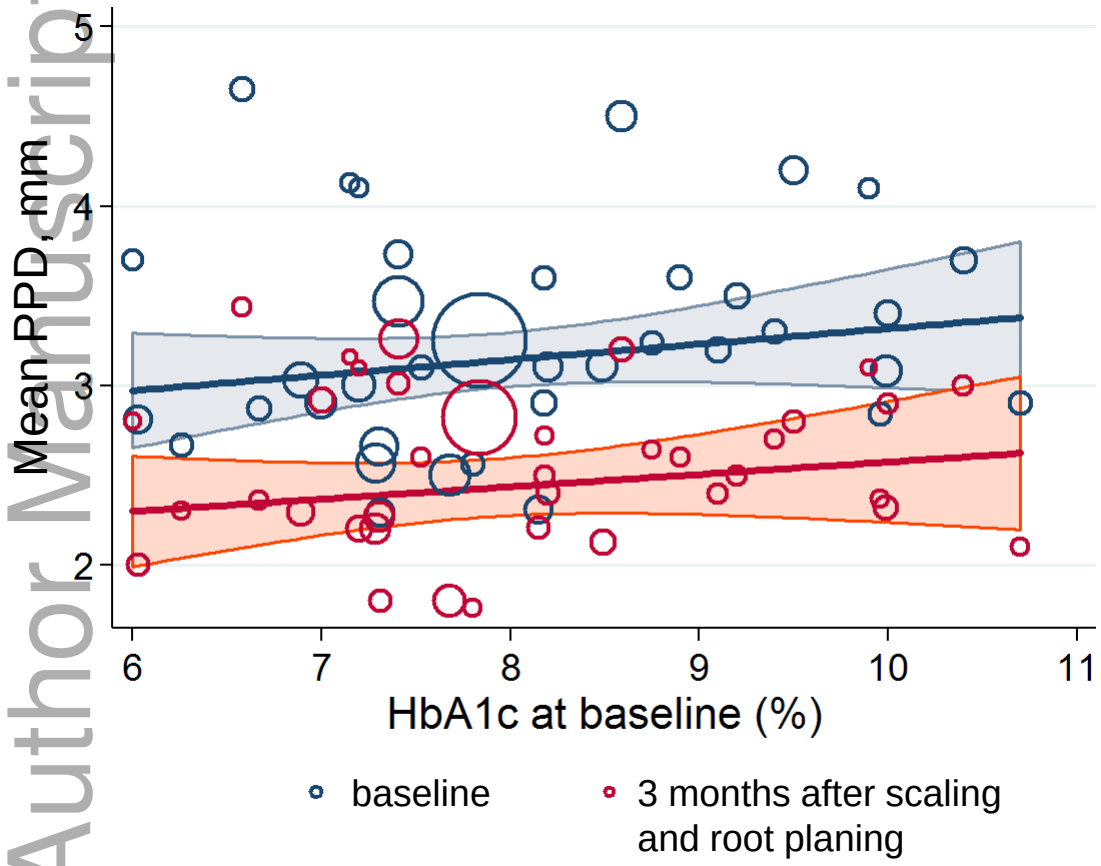
Figure 16



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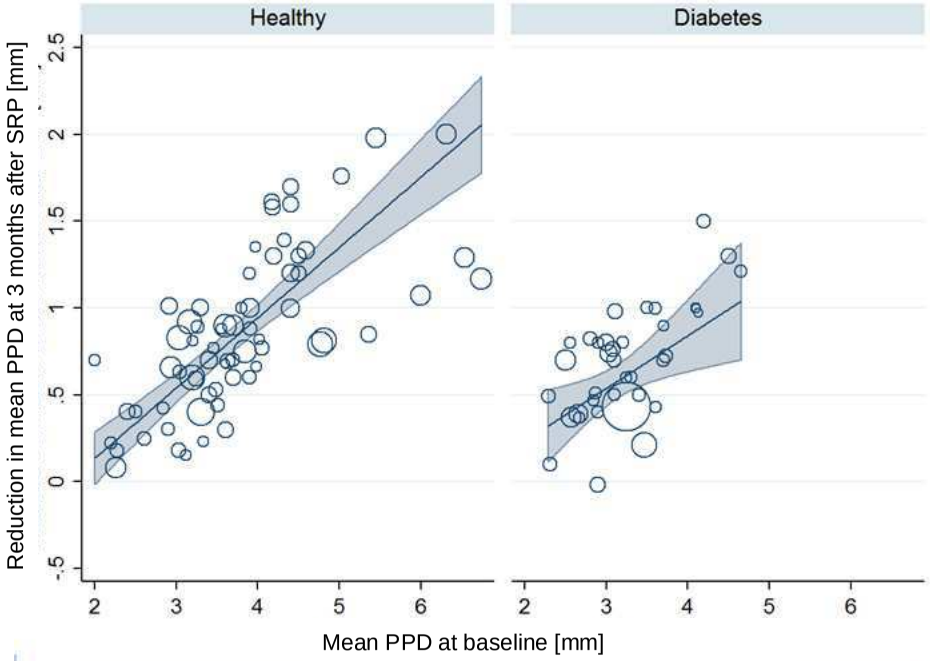

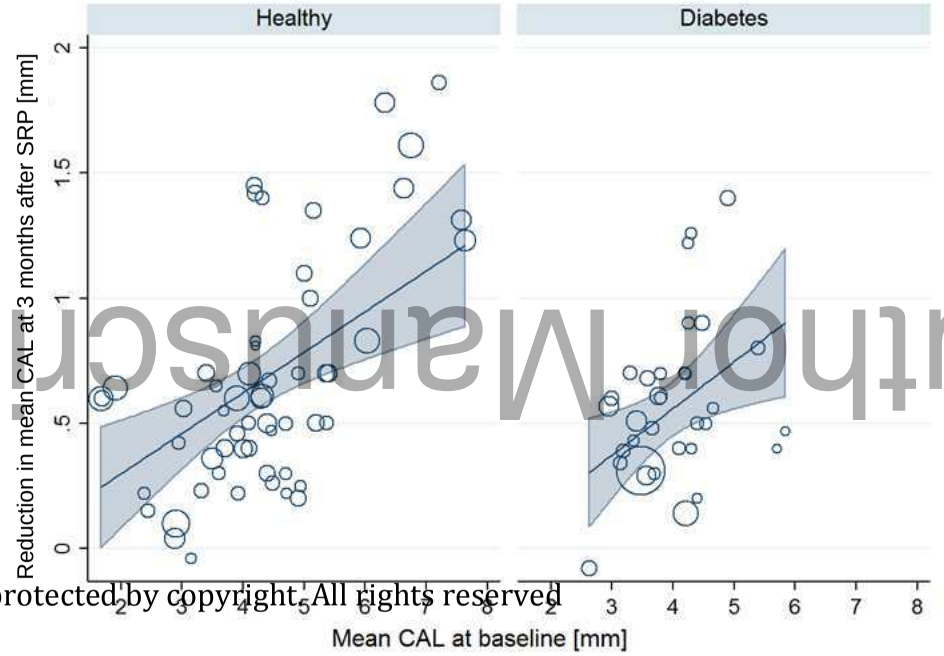

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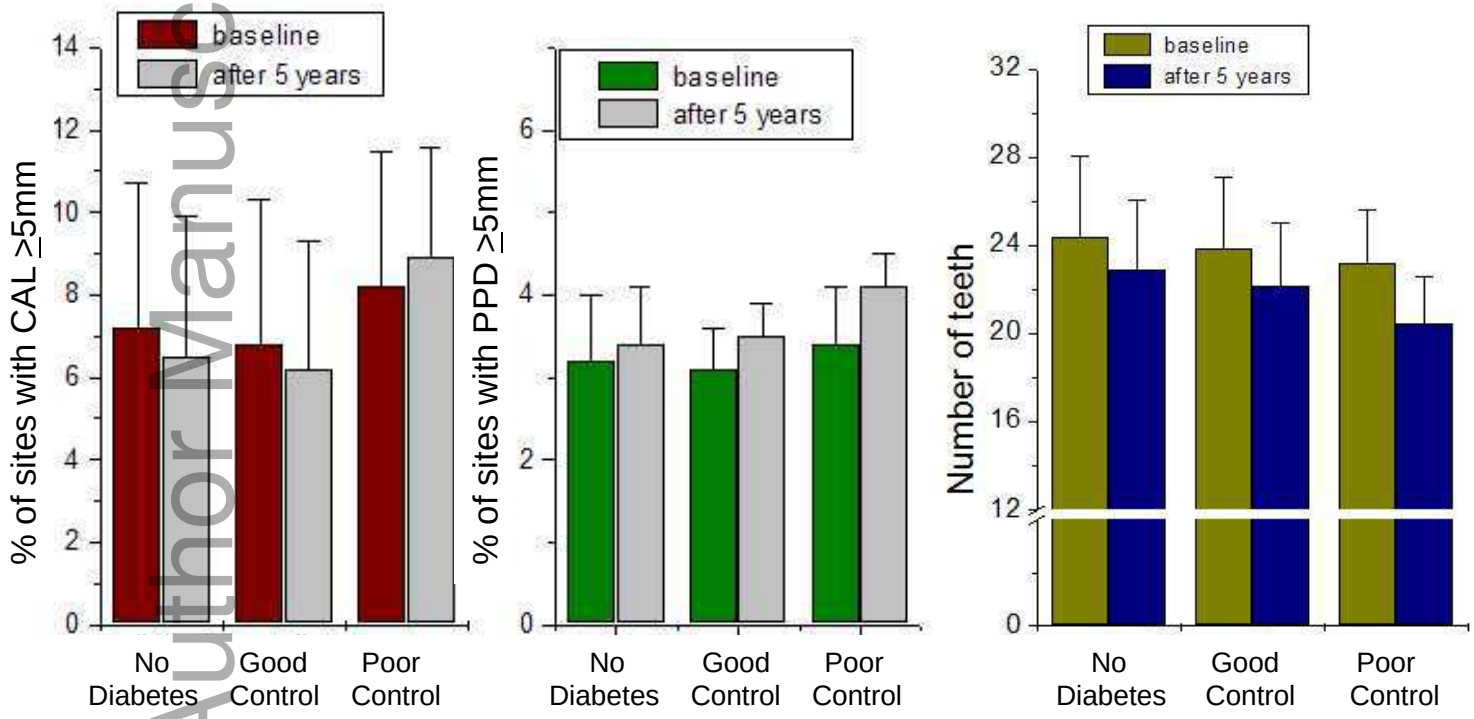
Figure 18



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