

Periodontal Infection and Glycemic Control in Diabetes: Current Evidence

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ABSTRACT

Both diabetes and periodontal diseases are common chronic diseases. *This article describes the current evidence regarding the relationship between periodontal infections and glycemic control in diabetes. In some individuals, the pathogenesis of diabetes as well as the state of poorer glycemic control appears linked with inflammation and infection. There are important characteristics of periodontal infection that suggest a biologically plausible link to systemic inflammation and adverse effects on glycemic control. There is also empirical evidence that suggests treating periodontal infection can lead to improved glycemic control. There still remains sufficient variation in the body of literature to recommend additional, large-scale definitive studies. However, the implications of treating periodontal infection on glycemic control may have important potential in managing diabetes and in reducing the burden of diabetes.*

TABLE 1:

Oral Health-Related Conditions Reported to be Associated With Diabetes

Periodontal diseases
Dental caries
Tooth loss
Oral candidiasis
Oral lichen planus
Xerostomia
Burning mouth syndrome
Alterations in taste

This article describes the current evidence regarding the relationship between periodontal infections and glycemic control in diabetes. The epidemiologic data are based on the United States, but the patterns of association are nevertheless becoming increasingly common in other parts of the world. The focus is on oral health and diabetes in the United States, but it reflects the emerging epidemic of diabetes in various parts of the world. This article covers diabetes, periodontal diseases, and insulin resistance, as well as how they might be interrelated through epidemiologic studies and plausible biologic mechanisms. Additionally, this article considers observational and clinical studies pertaining

to periodontal infection having an adverse effect on glycemic control.

There is very strong and consistent evidence that diabetes has an adverse effect on periodontal health.¹ Table 1 shows other oral health-related conditions which have been reported to be associated with diabetes but will not be considered in this discussion. The evidence is varied, but **stronger evidence exists for the relationship between diabetes and periodontal diseases than for any of the other oral health-related conditions.**

In the United States, diabetes is a very prevalent, common, chronic disease. Approximately 20.8 million people or 7% of the US population has diabetes,² and 30% of the people with diabetes have

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TABLE 2:**Prevalence of Diabetes by Race/Ethnicity Among People Aged 20 years, United States, 2005**

Race/Ethnicity	%
Non-Hispanic whites	8.7
Non-Hispanic blacks	13.3
Mexican Americans*	9.5
American Indians and Native Alaskans†	15.1
Asian Americans and Native Hawaiian or other Pacific Islanders	Up to 2X non-Hispanic whites

*Sufficient data are not available to derive estimates of the total prevalence of diabetes for other Hispanic/Latino groups.

†Among those who receive care from the Indian Health Service.

not been diagnosed. In the United States, the prevalence of type 2 diabetes is associated with age and minority status. Among people ≥ 60 years, the prevalence of diabetes is approximately 3 times greater than the prevalence for people of all ages.² Table 2 shows the distribution of diabetes prevalence among US minority populations. Several minority ethnic populations are more likely to have diabetes than non-Hispanic white individuals of similar age in the United States.²

Figure 1 shows the prevalence of diabetes by US state in 1994 and in 2003 as well as the dramatic increase in diabetes prevalence in 2003.³ This increase is most likely a result of changes in lifestyle, increased diabetes diagnosis, an increase in obesity prevalence, and a diminution in physical activity.

BURDEN OF DISEASE**Diabetes**

Diabetes imparts a tremendous burden associated with its complications. These

complications include heart disease and stroke, high blood pressure, visual impairment (leading to blindness), renal disease, nervous system disease, amputations, complications of pregnancy, and greater susceptibility to many other illnesses.² The monetary burden has been reported as approximately \$132 billion US dollars with \$92 billion in direct medical costs and \$40 billion in indirect costs (eg, disability, work loss, and premature mortality).²

Periodontal Disease

Periodontal disease is a chronic inflammatory disease of bacterial ideology. The importance of gram-negative pathogens becomes crucial in considering the relationships between periodontal disease and glycemic control. The local effects of the host response to periodontal infection include tissue destruction and, in severe cases, tooth loss. However, it is now believed that there may be additional systemic effects from periodontal disease.

Like diabetes, periodontal disease is a very common chronic disease among the

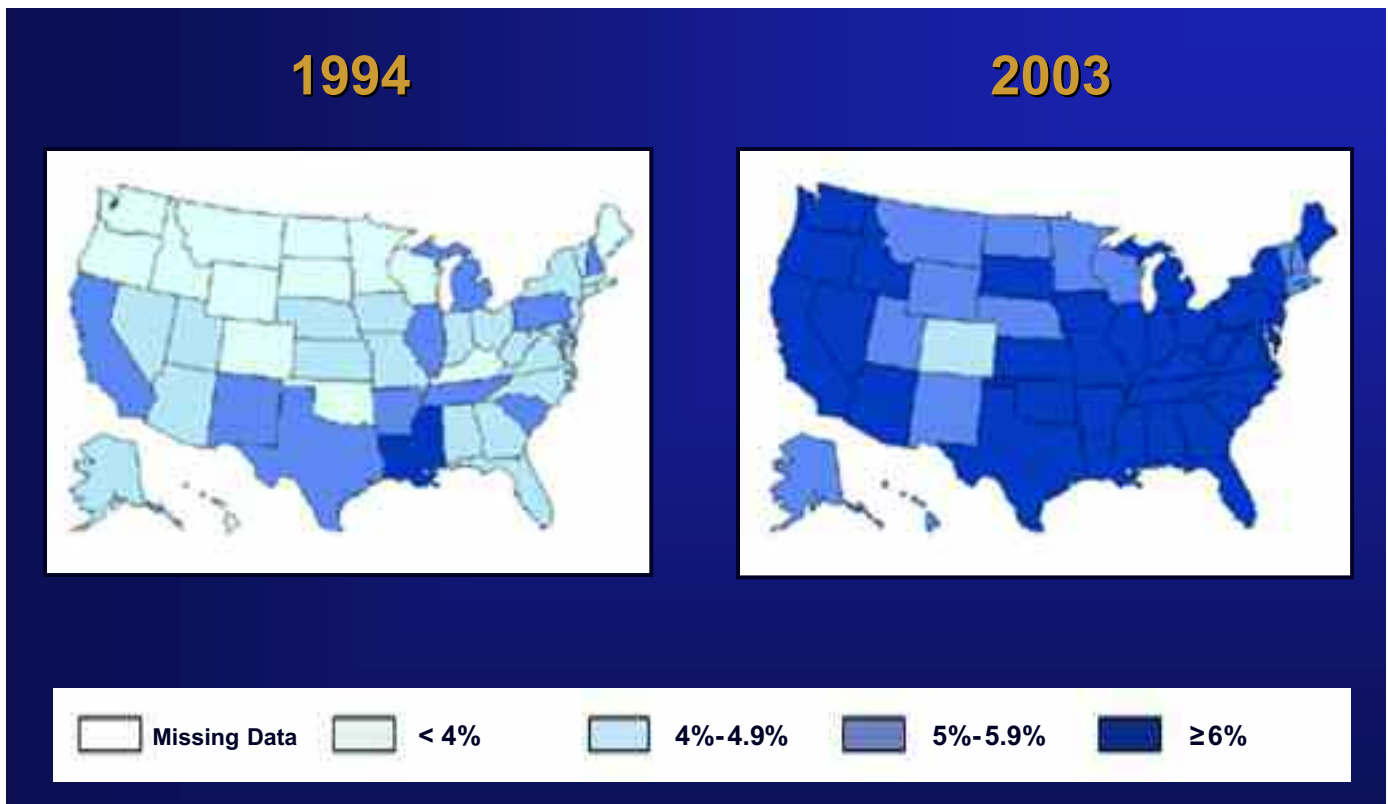


Figure 1 Age-adjusted prevalence of diagnosed diabetes per 100 adult population by state (United States, 1994 and 2003). Source: Centers for Disease Control and Prevention.³

Implications: Effect of Treating Periodontal Infection on Glycemic Control

- Glycemic control improvement
- Prevention, delay, or reduction in severity of complications
- Possibly preventing the development of diabetes itself

US population. Across all ages, >50% of the US population has gingivitis. The prevalence of severe periodontitis (measured by loss of periodontal attachment ≥ 6 mm) increases with age. On average, approximately 13% of the population has moderate or severe periodontitis.⁴

THE LINK

Why is it thought that diabetes and periodontitis are linked with regard to periodontitis influencing insulin resistance and glycemic control? There is a series of epidemiologic studies that provides support.⁵ Several epidemiologic studies show a relationship between inflammation and insulin resistance. In these studies, people with higher levels of inflammatory markers are more likely to have insulin resistance than those with lower levels.⁵ Insulin resistance is also a continuing problem in people with diabetes.

Inflammation and diabetes are related. There is an emerging body of evidence that suggests people with inflammation are more likely to acquire diabetes at some time in the future.⁵ Periodontitis and the acute phase response have been linked through observational studies,⁶ particularly with regard to heightened levels of C-reactive protein as well as in some treatment studies where treating periodontal disease has resulted in a reduction in C-reactive protein.^{7,8}

In inflamed periodontal tissues, there are increased levels of inflammatory mediators associated with tissue destruction, including tumor necrosis factor alpha (TNF- α), interleukin 6 (IL-6), interleukin 1 β (IL-1 β), prostaglandin E2, and matrix metalloproteinases.⁹ In addition to the local destruction, this inflammation involves increased permeability of the capillaries leading to potential portals to the systemic circulation for the inflammatory mediators as well as the products of the bacterial infection.

PERIODONTITIS AS A RISK FACTOR FOR CHRONIC SYSTEMIC INFLAMMATION

It is possible to conceptually integrate the clinical presentation of periodontitis as a chronic inflammatory condition with the current views of the role of inflammation in the pathogenesis of diabetes and coronary heart disease. Coronary heart disease is considered in this context because of the body of evidence supporting inflammation as a risk factor in the pathogenesis of coronary heart disease, and the recognition that diabetes is a risk factor for heart disease.⁵ It is increasingly recognized that sources of chronic inflammation and visceral obesity produce a generalized proinflammatory state, which includes chronic overexpression of cytokines and other inflammatory mediators.⁵ The linking hypothesis is that the host response to periodontal infection can be an important source of chronic inflammation, and a source for increasing the systemic burden of proinflammatory cytokines.

IL-6 and TNF- α are two of the proinflammatory mediators known to be produced in periodontitis. These mediators have been reported to be important in pathways for the pathogenesis of insulin resistance, coronary heart disease, and, more recently, diabetes. In one hypothesized pathway, IL-6 and TNF- α stimulate the acute phase response in the liver, resulting in the production of acute phase reactants, such as C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1.⁹ These acute phase reactants have been reported to contribute to insulin resistance, as well as to be risk indicators and risk factors for the prevalence and incidence of both coronary heart disease and diabetes in epidemiologic studies. Further, insulin resistance, as a component of the metabolic syndrome, is recognized as a risk factor in the

pathogenesis of both diabetes and coronary heart disease.⁵

PERIODONTAL DISEASE AND ITS EFFECTS ON GLYCEMIC CONTROL

Observational Studies

One observational study¹⁰ reported the effects of severe periodontal disease on glycemic control over a 2-year period in Pima Indians in the United States. The investigators found individuals with severe periodontal disease (as measured by radiographic bone loss $\geq 50\%$) were significantly more likely to have hemoglobin A1c (HbA1c) levels $>9\%$ (poorer glycemic control) than those who had better periodontal health (no radiographic bone loss $\geq 50\%$). In the follow-up study, all of the participants had HbA1c levels $<9\%$ at baseline. In multivariable analysis of the data for that study, the significant effect of severe periodontal disease on the incidence of poorer glycemic control persisted even while controlling for baseline HbA1c, which would normally be expected to correlate highly with the level of HbA1c at follow-up and hence potentially attenuate or eliminate the effects of weaker risk factors in multivariable models. Another study by Collin and colleagues¹¹ investigated older adults in Finland and found that people with advanced periodontitis were more likely to have higher HbA1c levels than those who had no or moderate periodontitis at follow-up.

Clinical Evidence

The most important evidence of the effect of periodontal disease on glycemic control can be derived from clinical studies involving treating periodontal disease and measuring subsequent changes in glycemic control. This body of evidence has been extensively reviewed

Summary

- Diabetes pathogenesis and glycemic control linked to inflammation and infection
- Common elements seen in periodontal infection and the diabetes/glycemic control/inflammation link
- Evidence that treating periodontal infections can lead to improved glycemic control

previously.^{12,13} Current evidence is mixed, with some evidence from clinical studies providing support for periodontal infection/severe periodontitis having an adverse, yet modifiable, effect on glycemic control,¹⁴⁻²³ although not all studies have reported an improvement in glycemic control after periodontal treatment.²⁴⁻²⁸ Reviewing the body of evidence in its entirety, it is premature to firmly establish that the treatment of periodontal disease is an effective intervention in improving glycemic control in either type 1 or type 2 diabetes. Additional rigorous, systematic study is warranted to test whether treating periodontal infections can be beneficial to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus.

Antibiotics

The methodology used in the studies in this body of literature varies in many ways and much of this variation has been reviewed previously.²⁸ Since that review, one important issue that has continued to evolve is the use of antibiotics. Several studies that reported a beneficial effect on glycemic control included the use of antibiotics in the protocol.^{14,16,18,20-22} There are some interesting points that can be taken from these studies, all of which used mechanical periodontal therapy in conjunction with antibiotics. The study by Rodrigues and colleagues²¹ used amoxicillin and augmentin as the antibiotic system and regimen. They found the most improvement in the placebo group, who did not receive the antibiotic. Two studies used locally delivered minocycline.^{20,22} The regimens were different in the two studies, but both reported an improvement in glycemic control. Additionally, Iwamoto and colleagues²⁰ reported significant reductions in serum TNF- α , fasting

immunoreactive insulin (a measure of circulating endogenous insulin in patients who were not receiving insulin therapy), and a significantly reduced homeostasis model assessment index (an indicator of insulin resistance).

There is also an emerging argument that there may not be a need for antibiotics' use in conjunction with mechanical periodontal therapy to improve glycemic control. Several studies report an improvement in glycemic control with mechanical periodontal therapy alone.^{15,17,19,23}

Other Sources of Variation in the Evidence

In reviewing this body of literature and considering the variation in results, there are additional important issues to consider. Among all of the studies, there are no standard criteria for the level of periodontal disease to use for inclusion. Most of the studies followed up on glycemic control after periodontal therapy at 3 months. However, some studies followed participants beyond 3 months. Other important sources of variation in the body of literature include the baseline level of HbA1c for study inclusion, the type of diabetes, the specific mechanical periodontal treatment regimen (eg, single session or multiple sessions, use of antimicrobial irrigation, inclusion of periodontal maintenance visits), the length of follow-up, the stability of the participants' diabetes medical management, measures of lipids and other biomarkers, and the role of self-care practices and products.

CONCLUSION

In some individuals, the pathogenesis of diabetes and the state of poorer glycemic control appear linked with inflammation and infection. There are important char-

acteristics of periodontal infection, which suggest a biologically plausible link to systemic inflammation and adverse effects on glycemic control. There is also evidence that treating periodontal infection can lead to improved glycemic control. There still remains sufficient variation in the body of literature to recommend additional, large-scale definitive studies. However, the implications of treating periodontal infection on glycemic control may have important potential in managing diabetes and in reducing the burden of diabetes.

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