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INVEST: The Escalation of Evidence to Support the Link Between Periodontal Disease and Cardiovascular/ Cerebrovascular Diseases

Abstract

There is accumulating research that supports a relationship between periodontal disease and cardiovascular disease (CVD) and cerebrovascular disease (stroke); evidence to support this link appears to be getting stronger. However, a direct cause and effect relationship has not been established. Untangling this mystery entails wading through a complicated web of multifactorial and complex biological relationships. Previous reports of periodontal disease's association with vascular diseases have yielded inconsistent findings, primarily because of differences in study design, the definition of periodontal disease, the outcomes that were studied, and factors that may have confounded the findings (ie, smoking). Two pieces of research that have been reported within the last year from the Oral Infections and Vascular Disease Epidemiology Study (INVEST) have garnered the attention of the scientific community on both the dental and medical side. This article provides a synopsis of those findings and challenges readers to consider how to incorporate this information into clinical practice.

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Much has been studied about the possibility that periodontal disease may influence the initiation and/or progression of cardiovascular disease (CVD) and cerebrovascular disease (stroke). In fact, there has been so much interest in uncovering a potential pathobiological relationship that the spiral of scientific curiosity now transcends the boundaries of dentistry—many members of the medical and biotechnology communities are joining the race for answers.[1-7]

In the late 1980s, researchers began to seriously speculate that inflammation from periodontal disease origin could influence the onset of CVD. In the genesis study, Eastern European researchers found that the incidence of myocardial infarction (MI) was higher within a group of male, Yugoslavian patients with worse periodontal health than that of the control patient group.[8] Editorial space will not permit discussion of the findings of the many subsequent case controlled studies that followed since that time. Needless to say, a great number of researchers have weighed in on the question of whether there is a relationship between periodontal disease and CVD and stroke.

Although most studies have supported an association between poor oral health and CVD and stroke, several epidemiologic studies found no such relationship.[9,10] With the contradictory nature of the emerging research, it became obvious to academics and researchers that it was necessary to create a consensus opinion on this proposed periodontal-systemic link.

The 2003 Workshop on Contemporary Science in Clinical Periodontics was held by the American Academy of Periodontology (AAP) to allow experts to carefully analyze this body of science and determine the strength of evidence to support an association between periodontal disease and the initiation/progression of atherosclerosis, CVD, stroke, and peripheral vascular disease (PVD). To arrive at their consensus opinion, the workshop participants performed an exhaustive literature search of more than 1,500 published, randomized, controlled clinical trials, and longitudinal, cohort, and case controlled studies that included human subjects who had been identified with atherosclerosis, MI, stroke, or PVD and who had oral conditions that included periodontal disease.[11] Of the 1,500 studies initially identified, the workshop participants filtered out all but 8 case controlled and 18 cross sectional reports to analyze.[11] However, what confounded the systematic reviews was that few of these studies used the same criteria for measuring periodontal disease. Consequently, the lack of common data sets made it impossible to perform a statistical comparison of data of the different studies.[11] However, the various studies were ranked according to the strength of the evidence supporting a link.[11]

The consensus of the AAP's 2003 Workshop on Contemporary Science in Clinical Periodontics was that there was a moderate level of evidence to suggest that periodontal disease is associated with cardiovascular disease.[11] It also was the consensus that additional large-scale, longitudinal epidemiologic and intervention studies would be necessary to validate the association between periodontal disease and CVD and to determine whether the association was causative or perhaps the result of etiologic factors common to both disease processes.[11]

The AAP concluded that there was insufficient evidence to support advising our patients that treatment of periodontal disease could prevent the onset or progression of atherosclerosis-induced diseases. However, growing research findings implicated infection, local and/or systemic inflammation and, possibly, autoimmunity in the formation of atherosclerotic lesions within blood vessels and that atherosclerosis was the major contributing factor in most cases of CVD and stroke.[11]

It is important to note that with the exception of 1 other published research study, all of these studies—including those analyzed in the 2003 Workshop on Contemporary Science in Clinical Periodontics—focused on increased risk for MI and stroke in relation to tooth loss.[12] Until recently, little was published relative to the precursor of CVD and stroke, namely atherosclerosis. Since the AAP's workshop proceedings were held, the evidence to support a link between periodontal disease and CVD may be escalating as a result of some recently published research.[13,14] Indeed, many of dentistry's leading minds and luminaries have been paying careful attention to 2 recently pub-

Learning Objectives

After reading this article, the reader should be able to:

- discuss the etiology of atherosclerosis and how it predisposes individuals to cardiovascular disease (CVD) and cerebrovascular disease (stroke).
- explain how periodontal disease may be a modifiable risk factor for atherosclerosis and resulting CVD and stroke.
- describe how the results of the Oral Infections and Vascular Disease Epidemiology Study (INVEST) may affect how dental hygienists practice.

lished landmark studies that, if verified by future research, may redefine our roles within the healing arts.[13,14]

A series of research findings called the Oral Infections and Vascular Disease Epidemiology Study (INVEST), first published in 2003, provide more profound evidence that periodontal disease may actually accelerate the development of atherosclerosis related diseases (ie, CVD and stroke) and provide direct evidence of a possible role that periodontal pathogens may have in the initiation of atherosclerosis.[13,14] Researchers of the INVEST studies "got it"—their reasoning seemed to be that because the first clinical manifestation of CVD often arises from atherosclerosis, unraveling the relationship between tooth loss and subclinical (undetected) atherosclerosis may better explain a potential pathway through which oral health may affect vascular diseases.[13]

This article attempts to provide a brief overview of the important findings of the INVEST studies cited above and to challenge readers to consider the significant implication of this research relative to its impact on public health. If further studies confirm the findings made in the 2 INVEST studies already published, it may be possible to help prevent or control the development of atherosclerosis in some people by treating their periodontal disease.[13,14] The repercussions of this are overwhelming because this has the potential to translate into a significant reduction in the incidence of CVD and stroke. To comprehend the significance of the INVEST studies, it is important that readers first understand the pathogenesis of atherosclerosis and how it predisposes individuals to CVD and stroke.

About Atherosclerosis

The term *atherosclerosis* comes from the Greek words athero (meaning gruel or paste) and sclerosis (meaning hardness).[15] The advancing atherosclerotic lesion progressively restricts the diameter of arteries and reduces the blood flow and oxygen supply to the brain, heart, and other vital organs that is manifested by the incidence of MI or stroke.[15] As a result, atherosclerosis is the primary cause of death and disability [CASEY: Is atherosclerosis the primary cause of CVD?] in the United States.[16,17] Atherosclerosis is a slow, progressive disease that may start as early as childhood.[15] In some people, atherosclerosis progresses rapidly in their 30s; in others, it does not become a threat until they're in their 50s and 60s.[15] The development of an atherosclerotic lesion is suspected to be a multifactorial and complex process and may possibly have a genetic basis.[15]

> Periodontal disease may actually accelerate the development of atherosclerosis related diseases.

Many scientists believe that atherosclerosis begins with inflammation-induced damage to the innermost layer of the artery.[15] When this inner layer is damaged over time, deposits of fats, cholesterol, platelets, and cellular debris accumulate in the walls of the arteries and form "atheromas" or plaques.[15] Eventually, this fatty tissue can erode the wall of the artery, diminish its elasticity, cause narrowing of the arterial lumen, and impair blood flow.[15] These deposits may stimulate the cells of the artery wall to produce other substances, which results in more accumulation in the innermost layer of the artery wall where the atherosclerotic lesion forms.[15] As these fat cells accumulate, many of them divide and additional fat builds up within and around these cells.[15] This often forms connective tissue and the innermost layer of the artery becomes markedly thickened.[15]

Severely restricted blood flow in arteries that connect to heart muscle leads to symptoms like chest pain.[15] Unfortunately, atherosclerosis shows no symptoms until flow within the blood vessel has become seriously compromised and complications such as heart attack or stroke occurs.[15]

Atherosclerotic plaque is a live tissue and when it is intensified by inflammatory conditions or other risk factors it may grow and become progressively unstable.[15] At some point, the plaque may fragment; as these fragments migrate downstream, conditions become ripe for MI and/or stroke.[15] Clots also can form around the plaque deposits, further interfering with blood flow and posing added danger if they break off and migrate to the heart, lungs, or brain.[15] Subsequently atherosclerotic plaque is a prerequisite of risk for the most common causes of stroke.[15]

Carotid intima-media thickness (IMT), an important marker of early atherosclerosis, is a measure of the carotid artery lining in areas that do not yet contain plaque but that often precede the development of more mature plaque.[15,18] Carotid IMT is a well established measure for assessing the extent of atherosclerosis and the risk for cardiovascular and end-organ (ie, brain) damage.[18] Carotid IMT has proven to be an independent risk factor for MI and stroke.[18] In some studies, increased carotid IMT was associated with a 4-fold greater risk of combined acute MI and stroke over 6 years.[19] As a result of these and other findings, increased carotid IMT is considered a mirror of the atherosclerotic burden and a predictor of subsequent cardiovascular events.[18]

Subclinical atherosclerosis and IMT are conditions that are extremely prevalent and not detectible without specific diagnostic testing.[15] In other words, there is a large percentage of the population who are asymptomatic for these conditions and who walk around unaware of the risk they have for serious cardiovascular events.

Measuring carotid IMT through carotid ultrasound detects the presence of atherosclerotic plaque, defined as an area of focal wall thickening.[14] The procedure is virtually harmless, painless, and widely available.[15]

> Atherosclerotic plaque is a prerequisite of risk for the most common causes of stroke.

Advances in imaging technology allows for greater preventive diagnostics and care, but unfortunately, most physicians still focus on diagnosing the cardiovascular crisis rather than averting it through preventive medicine.[15] The INVEST studies build a strong case for looking at periodontal disease as a modifiable risk factor for accelerating atherosclerosis and carotid IMT, resulting in an increased risk for life-threatening CVD and stroke.

An INVEST Overview

INVEST was designed to study the hypothesis that periodontal infections predispose individuals to accelerated progression of carotid atherosclerosis and, therefore, increased risk for stroke, MI, and CVD death.[13] The study is supported by the National Institutes of Health's National Institute of Dental and Craniofacial Research and its principal investigator is Moise Desvarieux, MD.[20] Desvarieux and colleagues will monitor the oral and cardiovascular health of a large, racially mixed group of people for at least 3 years (the study began in 2003).[20]

The study subjects were randomly selected by zip codes within a northern section of Manhattan in New York City. This methodology provided an initial sample of 711 participants and triethnic representation of 64% Hispanic, 21% black non-Hispanic, and 15% white non-Hispanic.[13] Other eligibility criteria include patients who[13]:

- are age ≥55 years at the time of the first in-person assessment,
- have no baseline history of stroke, MI, or chronic inflammatory conditions, and
- are able to be contacted by telephone and have the ability to come to the clinic.

During the baseline examination, researchers categorized dentate subjects according to the current extent of periodontal disease (measured by periodontal depth [PD]), and the cumulative extent of periodontal disease (measured by clinical attachment loss [CAL]).[13] The level of severity researchers defined as periodontal disease was ≥5 mm for PD and ≥4 mm for CAL.[13] Disease extent was defined by the percent of periodontal sites meeting the above severity criteria for PD and CAL.[13] These severity criteria are slightly higher than several previously reported studies, which defined PD of ≥ 4 mm and CAL of ≥3 mm as the threshold for diagnosing periodontal disease.[20]

The INVEST researchers pointed out that if those criteria had been used in place of their more conservative criteria, about 90% of the INVEST study population would have been classified as having more serious disease.[20] This would have a significant compounding effect on the findings of INVEST. The assessment of periodontal status also included the presence or absence of dental plaque, and a visual check for caries and mobility. Tooth loss was categorized as[13]:

- 0 to 9 missing teeth
- 10 to 19 missing teeth
- 20 to 31 missing teeth
- no teeth (edentulous)

Study participants also were assessed for risk factors through interviews, medical records, physical and neurological examination, and fasting (overnight) blood specimens. Sociodemographic characteristics and risk factors that were recorded include hypertension, diabetes, hypercholesterolemia, PVD, transient ischemic attack, cigarette smoking, alcohol use, and cardiac conditions such as MI, coronary artery disease, angina, congestive heart failure, arterial fibrillation, other arrhythmias, and valvular heart disease. Subjects also completed a battery of tests to assess their individual functional status (ie, physical activity levels and social isolation variables).

As of this issue's publishing date, 2 articles, which will be referred to in this article as INVEST 1 and INVEST 2, reporting various findings of this important epidemiologic study have been published.[13,14]

INVEST 1

INVEST 1 hypothesized that in older adults, edentulism and loss of more than a few teeth mark past periodontal disease not visible in current observation because teeth removal was the result of either severe infection or the elimination of the site of infection.[13] Specifically, researchers investigated the extent to which tooth loss corresponded with current and cumulative measures of periodontal disease.[13] In addition, the researchers examined whether there was a relationship between the surrogate markers of periodontal disease (ie, PD, CAL, and tooth loss) and the presence of carotid artery plaque.[13] To determine whether there was a correlation, both right and left carotid arteries on all study participants were assessed by carotid ultrasound.

The findings of INVEST 1 include:

1. Regarding the relationship between tooth loss and clinical measures of periodontal disease, the greater the number of teeth lost, the greater the extent of severe periodontal disease.[13] Across increasing levels of tooth loss, there was a consistent increase in the age-adjusted proportion of sites with both severe CAL and deep PD.[13] The researchers have postulated that although individuals' loss of the first teeth may be related to caries or orthodontic reasons, edentulism or loss of more than just a few teeth in older adults more likely reflects periodontal disease.[13] The researchers maintain that their data give credence to the supposition that tooth loss may be a valid and more telling marker of long-term cumulative periodontal disease in some populations.[13]
2. Regarding the relationship between conventional measures of periodontal disease, tooth loss, and carotid artery plaque, the percentage of participants with any carotid artery plaque present was approximately 55% at all levels of both current and cumulative measures of periodontal disease extent.[13] The correlation of these findings with the different categories of tooth loss include[13]:
   - 45% of participants with 0 to 9 missing teeth had carotid artery plaque.
   - ≥60% of participants with ≥10 missing teeth had carotid artery plaque.

- Even after adjustments for standard CVD risk factors, social isolation, oral hygiene, years of residence, and physical activity, the prevalence of carotid artery plaque barely changed.
- When looking at the subgroup of smokers, the smoking status (ie, never, ex, or current), number of packs per year, time since cessation, number of cigarettes per day, and smoking duration did not change the prevalence of carotid plaque. This is especially interesting because smoking is widely recognized as a risk factor for atherosclerosis.[15]
3. The researchers put forth several other suppositions about edentulous patients that are very disconcerting: "when one loses teeth previously affected by periodontal disease, the evidence of the cumulative effect of periodontitis is removed while the systemic damage may partly persist" and "…systemic damage may not be entirely reversible…"[13] These suppositions have tremendous ramifications for clinicians who treat significant numbers of edentulous or nearly edentulous patients.

INVEST 2

Using the same study population referenced in INVEST 1, INVEST 2 studied the relationship of microbes—both periodontal pathogens and those microbes that are not recognized as being etiologically significant in periodontal disease—and the presence of thickened carotid IMT.[14] The researchers specifically investigated whether carotid IMT correlated with[14]:

- the cumulative microbial burden in the periodontium.
- the burden of specific bacteria causative of periodontal disease.
- the relative predominance of a greater proportion of bacteria that are periodontal pathogens over other bacteria in the subgingival plaque.[CASEY: Edits okay?]

The researchers' hypothesis was that those bacteria causally related to periodontitis would correlate with increased IMT, and that no such relationship would be found for those bacteria that were not causative in periodontal pathogenesis.[14]

To test their hypothesis, a mean of 7 subgingival plaque samples were collected from the 2 most posterior teeth in each quadrant of all study participants.[14] There was a total of 4,561 bacterial plaque samples from each study participant.[14] The selected microbial strains included species currently considered to be etiologically linked with periodontal diseases or frequently encountered in pathological periodontal conditions, commonly accepted as being associated with periodontal disease, and primarily associated with healthy periodontal conditions.[14]

The protocol for carotid IMT scanning consisted of study participants undergoing scanning of the carotid arteries longitudinally in 3 segments, which is further described in the study methodology.[14] Carotid IMT was calculated as a composite score that included the mean of 12 sites of the various segments.[14] A risk assessment was performed.[13,14] All analyses were adjusted for age, race/ethnicity, gender, education,

body mass index, smoking, diabetes, systolic blood pressure, and low-density lipoprotein and high-density lipoprotein cholesterol.[13,14]

The findings of INVEST 2 include[14]:

- Those bacteria causally related to periodontitis are associated with increased IMT, whereas other bacteria are not. This finding would provide even greater support for a possible direct role of some infections in the pathogenesis of atherosclerosis.
- After adjusting for conventional risk factors, the mean carotid IMT increased with rising dominance of the etiologic bacterial group within the microbiological niche. Patients with oral bacteria populations that were dominated by bacteria causative to periodontal disease over other oral bacteria had thicker IMT after adjusting for conventional risk factors.
- White blood cell values tended to rise with both increasing levels of bacteria causative to periodontal disease and increased carotid IMT.
- No relationship between CRP and either IMT or the bacteria causative to periodontal disease was found. This was consistent throughout the study.

It appears that the pathogens etiologically related to periodontal disease may be driving increased carotid IMT.[14] Collectively, these findings strengthen the hypothesis that oral infections, specifically periodontal pathogens, may contribute to the relative incidence of CVD. These findings also increase evidence supporting that the microbiological burden is an important factor in the formation of atherosclerotic lesions. The bacteria implicated in the INVEST 2 findings are common pathogens of periodontal infection. Subsequently, findings of this study appear to reinforce the supposition that these bacterial pathogens can extend to the vasculature via release of cytokines, imitation of certain molecules, repeated bacteremias, or a hyperinflammatory response to a remote assault. But how do we apply this information in everyday dentistry?[14]

It appears that the pathogens etiologically related to periodontal disease may be driving increased carotid IMT.

What to Do with INVEST

Can we really tell our patients that the more teeth they have lost, the more likely they are to have advanced periodontal disease, undetected atherosclerosis, and increased risk for heart attack or stroke? The findings of the first 2 published INVEST studies seem to indicate that, in fact, a significant number of our patients who are 55 years and older may have atherosclerosis that has not been detected or may be at risk for carotid IMT as a result of undiagnosed and/or untreated periodontal disease. It is staggering to consider that many of the patients we see everyday could be at increased risk for MI or strokes because of undiagnosed and asymptomatic atherosclerosis that was accelerated by chronic periodontal infection.

By treating their periodontal disease, can we prevent or control our patients' development of vascular diseases and, by association, decrease their risk for MI and strokes? We don't have the longitudinal evidence or intervention studies to prove that claim at this time. However, it is this author's opinion that periodontal disease should be added to the list of risk factors (ie, diabetes, obesity, high cholesterol, kidney disease or dialysis, high-fat diets, and familial history of CVD, stroke, and hypertension) for atherosclerosis.

Heart and blood vessel diseases and conditions claim close to 100,000 lives annually.[21] More than 12 million Americans have experienced a heart attack, angina, or both.[21] These individuals have a 1.5 to 15 times greater risk of illness and death compared with the general population.[21] In the United States, 700,000 strokes occur each year and someone dies of stroke every 3 minutes.[15]

Even if periodontal disease treatment influenced the onset and/or severity of only a small percentage of cases of these atherosclerotic-induced diseases, this could translate into significant numbers of saved lives and could enhance the quality of life for older adults.

If the findings from the INVEST studies are confirmed, dental professionals may have an unprecedented opportunity to make a significant impact on the prevalence of CVD and stroke, starting with one patient at a time. This is how we change lives. **COH**

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1. Athero means:
   a. from the blood.
   b. from the city of Athens.
   c. gruel or paste.
   d. little mountains.

2. Sclerosis means:
   a. blocking.
   b. hardness.
   c. narrowing.
   d. roughness.

3. Atherosclerosis is a slow, progressive disease that may start as early as:
   a. age 30.
   b. age 40.
   c. age 50.
   d. childhood.

4. Many scientists believe that atherosclerosis begins with inflammation-induced damage to the:
   a. arteriole innervation.
   b. capillary plexus.
   c. coronary arteries.
   d. innermost layer of the artery.

5. Atherosclerotic plaque is:
   a. a live tissue.
   b. primarily made of cholesterol.
   c. radiolucent.
   d. radiopaque.

6. What is an important marker of early atherosclerosis?
   a. bleeding on probing
   b. carotid intima-media thickness (IMT)
   c. shortness of breath
   d. vascular hormone blood levels

7. In the INVEST studies, the level of severity researchers defined as periodontal disease was:
   a. ≥3 mm for periodontal depth and ≥2 mm for clinical attachment loss.
   b. ≥4 mm for periodontal depth and ≥3 mm for clinical attachment loss.
   c. ≥5 mm for periodontal depth and ≥4 mm for clinical attachment loss.
   d. ≥6 mm for probing depth and ≥5 mm for clinical attachment loss.

8. In INVEST 1, what percent of participants with ≥10 missing teeth had carotid artery plaque?
   a. ≥20%
   b. ≥40%
   c. ≥60%
   d. ≥80%

9. INVEST 2 studied the relationship of:
   a. DNA and the presence of thickened carotid IMT.
   b. heredity and the presence of thickened carotid IMT.
   c. microbes and the presence of thickened carotid IMT.
   d. viruses and the presence of thickened carotid IMT.

10. The bacteria implicated in the INVEST 2 findings are:
   a. common pathogens of periodontal infection.
   b. gram-negative.
   c. gram-positive.
   d. penicillin susceptible.

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