

Looking at the Periodontal-Systemic Disease Connection

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Studies within the past ten years have suggested an association between periodontal disease and the likelihood of delivering preterm, low-birthweight babies, developing cardiovascular disease, and having difficulty controlling blood sugar levels in people with diabetes. Some studies have also linked periodontal disease to respiratory infection in people with pulmonary problems. The Inside Scoop recently spoke with Bruce Pihlstrom, D.D.S., M.S., Acting Director of NIDCR's Division of Clinical Research and Health Promotion, about the Institute's clinical research on periodontal disease and its relationship to systemic disease.

Periodontal Disease and Preterm Birth

What led researchers to believe that women with periodontal disease may be at risk for delivering preterm, and/or low-birthweight babies?

In the mid-1990s there were some studies by researchers at the University of North Carolina (UNC) that compared the birth outcomes of women with periodontal disease to those of women without periodontal disease. The studies showed that women who had periodontal disease were more likely to deliver preterm and/or low birthweight (PLBW) babies. These observational studies, so-called because they didn't involve treatment, were among the first to bring this association to light. Additionally, the UNC researchers did studies in hamsters where they found that maternal exposure to by-products of periodontal bacteria during pregnancy had harmful effects on the fetus.

There have also been a couple of clinical trials -- particularly in South America. And those showed that treating periodontal disease resulted in fewer adverse birth outcomes in terms of PLBW. Those were the first intervention studies. A team of researchers in the U.S. also did a pilot interventional study. They found some trends that suggested periodontal disease therapy was associated with a reduced incidence of preterm birth. However, these intervention studies were either relatively small or not designed to determine whether treating periodontal disease would reduce the risk of delivering preterm, low-birthweight babies.

There are also studies that have found no greater risk of pregnant women with periodontal disease delivering PLBW babies.

What research is NIDCR sponsoring to try to clarify the relationship between periodontal disease

in pregnant women and the risk of delivering PLBW babies?

NIDCR is investing in the neighborhood of \$20 million on two independent, multi-center clinical trials on periodontal disease in pregnant women and preterm birth.

These large interventional studies, or clinical trials, are necessary for telling us whether treating periodontal disease in pregnant women can reduce the incidence of preterm birth. Some of the earlier, observational studies have shown us that there's an association, but these studies did not prove the association was causal.

In the NIDCR clinical trials, study participants are randomly assigned to one of two groups, either a periodontal treatment group or a delayed treatment [after delivery] group. The researchers will determine whether there is a difference between the two groups in rates of delivering preterm or low-birthweight babies.

Both NIDCR clinical trials were started within the last few years; one is recruiting 800 patients and the other is recruiting 1800 patients. The OPT -- the "Obstetrics and Periodontal Therapy Study," with 800 patients, will complete enrollment in a month or two. This study involves women from Jackson, Mississippi; Harlem in New York City; Lexington, Kentucky; and Minneapolis, Minnesota. The results of that trial should be available in 2006.

The second study started a little bit later and involves more patients, so it's not slated to be finished for a few more years. This second one is called MOTOR -- the "Maternal Oral Therapy to Reduce Obstetric Risk" study. It's taking place in San Antonio, Texas; the University of Alabama at Birmingham; and Duke University in North Carolina.

So we can't say that periodontal disease causes preterm birth or that treating periodontal disease will lower your risk of delivering a PLBW baby?

Right now, there's no proof that periodontal disease causes preterm birth or that preventing or treating periodontal disease will result in a lower incidence of delivering preterm or low-birthweight babies. We'll have to wait and see what these clinical trials tell us.

Periodontal Disease and Cardiovascular Disease (Heart Disease and Stroke)

What led researchers to believe there is an association between periodontal disease and cardiovascular disease?

Observational studies -- the same thing really as the PLBW link. Researchers looked at people with periodontal disease and found that they had a higher risk of heart disease. There were also some animal studies in which researchers injected periodontal bacteria into rabbits; they found the animals developed heartbeat irregularities and cardiac ischemia, or insufficient blood flow to the heart. But like the PLBW issue, there are conflicting data. There are some studies in humans that have shown an association between periodontal disease and cardiovascular disease and some that have not.

The evidence continues to mount with the observational studies, but the observational studies

don't give a definite answer on whether the association is causal--that is, whether periodontal disease causes cardiovascular problems. Interventional studies, or clinical trials, are needed to clarify the relationship.

What research is NIDCR doing to learn more about the relationship between periodontal disease and cardiovascular disease?

We're supporting additional observational research to better characterize the issue, but we are also sponsoring a pilot clinical trial to determine the feasibility of doing a larger clinical trial on this topic.

In the pilot study, called PAVE or "Periodontitis and Vascular Events," researchers are studying patients who have had a cardiovascular event and who also have periodontal disease. The long-term goal is to determine whether periodontal therapy can reduce the incidence of a second cardiovascular event. This study won't give us a final answer, but it will help us learn whether there will be problems with enrollment or other issues in launching a larger study. The pilot study is in the process of finishing up now.

Two recent studies produced some interesting findings on the link between periodontal disease and cardiovascular disease. In a paper that appeared early this year in the journal *Circulation*, NIDCR grantees and others reported that people who had higher levels of bacteria in their mouths also tended to have thicker carotid arteries, which is an indicator of cardiovascular disease. This study points to a more direct relationship between periodontal disease and heart disease. ([Click here to view the NIDCR news release about the paper in *Circulation*](#)).

In another paper, which appeared in the July 5, 2005 issue of *Circulation*, NIDCR grantees found that the systemic antibody response to periodontal bacteria was associated with coronary heart disease. (See the NIDCR "Science News in Brief" item dated July 13, 2005).

What are the challenges involved in studying the relationship between periodontal disease and cardiovascular disease?

First, a clinical trial of periodontal disease and its effect on cardiovascular health is a difficult study to do. If you randomly selected 40-year-olds with periodontal disease from the general population, you wouldn't have any idea how many, or if any, of them would ever have a heart attack or stroke. And it would not be ethical to do a clinical trial in which periodontal treatment was withheld for an indefinite period from half of the subjects.

So you probably need to do the trial with people who have already had a heart attack, because you're more likely to find the cause-and-effect relationship in that population. We know that, statistically, 3-7 percent of these people will have another cardiovascular event in the near future.

Conversely, in the preterm birth studies, 36-40 weeks after becoming pregnant there's definitely going to be an event for all the patients. Whether it's a birth, miscarriage etc., something is going to happen. With the heart disease study, you don't know whether people will ever have a cardiovascular event. Also, in the preterm birth studies you only have to delay treatment a few

months in the delayed-treatment group -- it isn't even nine months since they start the study in their second trimester. They're also being monitored, so that if anyone experiences progressive disease, they can be treated immediately.

We'll know more about the periodontal disease-preterm birth issue from the OPT trial next year. With the heart disease studies, I wouldn't be surprised if the discussion goes on for another 10 years or longer. We may never be able to precisely define the relationship; but there may be more and more data from observational studies that might eventually lead to a public health recommendation. However, we can't make any recommendations right now about treating periodontal disease to prevent preterm birth or cardiovascular disease.

Another challenge in studying the relationship between periodontal infections and cardiovascular disease is teasing out the effects of shared risk factors for both diseases, especially smoking. Smokers make up a large percentage of the participants in cardiovascular disease-periodontal disease observational studies. So how much of the observed association with heart attack might be due to periodontal infection as an independent risk factor and how much might result from smoking? That's something we still need to clarify.

Periodontal Disease and Diabetes

If you have diabetes are you more likely to get periodontal disease?

Yes. Diabetes does make you more susceptible to infection – any infection – including periodontal disease. And there is evidence that people with diabetes have more periodontal disease.

There also seems to be some evidence of the relationship going the other way -- that if you control periodontal disease, it may help you control your blood sugar.

Having an infection, including periodontal disease, can impair the body's ability to process and/or use insulin. So the theory is that if you control the infection, it might be easier to control blood sugar.

We have one pilot study on this topic. Researchers are looking at people with diabetes who are having difficulty controlling their blood sugar and who also have periodontal disease. They are treating the periodontal disease to see if the treatment results in improved control of blood sugar levels. This study is finishing up and there are investigators who are going to propose similar studies.

What are the challenges in determining whether controlling periodontal disease will result in better blood sugar control?

The Diabetes Control and Complications Trial found that 'intensive' control of blood sugar

reduced the risk for eye, kidney, and nerve disease compared to those using the 'standard' control. So if you are under intensive control, you wouldn't necessarily expect treating periodontal disease to bring down the blood sugar levels further. However, there are ongoing studies to see if it's feasible to do multi-center, interventional studies on this topic.

What led researchers to think there was any relationship between periodontal disease and diabetes?

For at least 50 years periodontists have felt that people with diabetes tended to have more severe periodontal disease and the bulk of the research does show an association between the two diseases. Several studies have shown that the more poorly controlled the diabetes, the more severe the periodontal disease is likely to be.

Periodontal Disease and Respiratory Infection

Isn't there some evidence that you can develop respiratory infection from inhaling periodontal pathogens?

Periodontal disease has been associated with pulmonary infections in people who are hospitalized or are in extended care facilities. Here again, there are no studies that have shown cause and effect. There are some studies in the pipeline looking at whether you can prevent respiratory problems by controlling dental plaque, particularly in patients who have existing breathing problems. NIDCR just started a study on this topic.

So to conclude, we can't tell people that periodontal disease causes preterm birth or heart disease, or results in difficulty controlling blood sugar levels or causes respiratory infections. Nor can we say that preventing or treating periodontal disease will help you avoid these conditions?

That's right. At this time, we can't say whether or not periodontal disease causes any of these conditions or whether treating periodontal disease will prevent them. But we can tell people to treat periodontal disease for its own sake -- to avoid tooth loss and to maintain oral comfort and function.

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