

Drug reduces gum disease, risk of osteoporosis, heart disease in women

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Dr. Lorne Golub, Distinguished Professor at Stony Brook University in New York, reviews data with Dr. Hsi-ming Lee, who directs Golub's lab (seated, at center), and doctoral student Muna El-Barkie (standing, at right). Credit: Jeanne Neville/Stony Brook University

(PhysOrg.com) -- New research has shown that a federally approved pharmaceutical for treating periodontal disease also significantly reduces risk of osteoporosis and cardiovascular disease in postmenopausal women.

A drug approved by the U.S. [Food and Drug Administration](#), or FDA, for treating [periodontal disease](#) also significantly reduces risk of [osteoporosis](#) and cardiovascular disease in postmenopausal women, new research has found.

In addition, the drug significantly raised levels of "good" [cholesterol](#) among women more than five years postmenopausal – the first medicine ever to be shown to do so.

University of Arizona cardiologist Dr. Marvin Slepian co-authored the study, which was the cover story this month in the [Journal of the American Dental Association](#).

As a source of systemic inflammation, chronic periodontal disease, a disease of the gums and underlying tooth supporting structures that is commonly known as "gum disease," could be a primary cause of chronic inflammation that leads to cardiovascular disease.

Previous research has linked cardiovascular disease, which is the leading cause of death in postmenopausal women, with persistent infection of the gums. "This study goes further and looks at the effect of reducing inflammation caused by infection on both oral and systemic consequences such as heart disease," said Slepian.

"This has a lot of implications," said Slepian, and added that with the drug's ability to reduce inflammation caused by periodontal disease, "we could also have an impact on the consequences of inflammation throughout the body such as the vulnerability of atherosclerotic plaque, the blockage of the artery, which is the pathology associated with coronary artery disease."

The initial version of the drug has its origins in the late 1940s with the development of the antibiotic family known as tetracyclines.

When Dr. Lorne Golub, State University of New York Distinguished Professor at Stony Brook University and a primary inventor of the newer formulations of the drug, discovered that tetracycline has the capacity to block collagen and tissue-destructive enzymes known as matrix

metalloproteinases, or MMPs, produced by the body's cells and tissues, he speculated that it could be used to treat multiple chronic diseases caused by the breakdown of body tissues because of the action of MMPs.

But there was a hurdle to be overcome: To effectively treat chronic disease, the drug would have to be administered over long periods of time, which can't be done with antibiotics because of side effects such as disrupting the balance of intestinal bacteria and overgrowth of bacteria that are antibiotic-resistant.

"The challenge," said Golub, "was to develop new compositions of the drug so that it was no longer antibiotic and could be administered to patients with chronic diseases for long periods of time."

The researchers were undaunted. They identified a binding site for calcium and zinc on the tetracycline molecule that is responsible for the drug's enzyme-inhibitor activity, and is different from the chemical side-chain that has antimicrobial properties.

"We chemically modified the drug to eliminate the side-chain needed for antibiotic activity, so that it lost the antibiotic site but retained the active site needed to counteract the harmful enzymes," said Golub.

Using doxycycline, the most potent of the tetracyclines as enzyme inhibitors, Golub created new formulations of the drug that could be administered not as an antibiotic but as a treatment for chronic inflammatory diseases. The result is the pharmaceutical known as subantimicrobial-dose-doxycycline, or SDD.

In addition, he and his colleagues developed a new series of drugs called the chemically-modified tetracyclines, or CMTs, which lack the antimicrobial side chain. One of these, CMT-3, is the first such drug

administered to humans and has showed evidence of efficacy treating patients with a type of cancer, Kaposi's sarcoma, where it acted as an inhibitor of new blood vessel formation that feeds the cancer.

"So we found a whole new use for this old family of drugs which had nothing to do with their antibiotic activity," said Golub, "and which we believe is even more important than their antibiotic activity."

SDD is the only drug approved by the FDA for treatment of chronic inflammatory periodontal disease. A sustained-release version of SDD is also FDA-approved for treatment of a chronic inflammatory skin disease known as Rosacea, and there is evidence that SDD inhibits bone loss in postmenopausal women with osteoporosis and could be beneficial for treating arthritis and other collagen-destructive diseases.

Periodontal disease results from localized bone loss around the teeth, while osteoporosis results from systemic bone loss that leads to skeletal degradation and fractures.

In the seven-year study funded by the National Institute of Health, or NIH, the scientists teamed up with researchers at the University of Nebraska to test whether SDD, already approved for treatment of bone loss in periodontal disease, also had any effect of reducing systemic bone loss.

The researchers randomly assigned SDD or placebo tablets in a double-blind study to 128 [postmenopausal women](#) with periodontal disease and osteopenia, the precursor to osteoporosis, for a two-year clinical trial period.

The study's results showed that inflammation and collagen-destructive enzymes due to periodontal disease were reduced significantly in women who took SDD tablets.

In addition, these women showed significantly reduced blood levels of molecular biomarkers of bone destruction that are indicators of systemic osteoporosis.

"The drug not only reduced their local periodontal disease over a two-year time period," said Golub, who is one of the principle investigators of the NIH-funded studies. "But also reduced risk factors for bone loss around their hips and spine."

Osteopenia, a precursor and milder form of osteoporosis, doesn't require medication. "We were reducing the risk of conversion of osteopenia to osteoporosis, which is typically treated with bisphosphonates which can produce side effects," said Golub.

A major benefit of SDD is that it has minimal side effects, said Slepian. The hope is that with SDD, doctors will be able to prevent development of osteoporosis without putting patients at risk for debilitating side effects.

The researchers also found highly significant reductions in the blood levels of the biomarker known as C-reactive protein, a chemical molecule that indicates impending cardiovascular disease. "Elevations in C-reactive protein may be even more important than elevations in cholesterol as risk factors of [cardiovascular disease](#)," said Golub.

And there was yet one more surprise: Women more than five years postmenopausal who took SDD tablets for two years showed significantly increased blood levels of high-density lipids, known as HDL cholesterol or "good" cholesterol. HDL cholesterol is known to reduce risk of heart attack.

No major drugs exist today to raise good cholesterol except Niacin, Slepian said, which is very hard to take and can have uncomfortable side

effects for many individuals.

"We're taking this to the next level to understand the mechanism," said Slepian.

HDL cholesterol has a core molecule that can be degraded by the same collagen and tissue-destructive enzymes that lead to osteoporosis and periodontal disease. The researchers believe that when SDD blocks the activity of these enzymes, the MMPs, reducing periodontal disease and risk of osteoporosis, it is also providing protection for the core molecule of HDL.

The collaboration among universities and departments that made the study possible is an essential element of scientific and medical progress, said Slepian: "This is an example of good innovation."

Provided by University of Arizona

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