

Miracle berries: how blueberries can improve bone health

Connie Weaver, PhD, is Distinguished Professor and Head of the Department of Nutrition Science, Director of the WGHI (Women's Global Health Institute), and Deputy Director of the Indiana CTSI (Clinical and Translational Sciences Institute) at Purdue University. As part of the collaborative 'Berries and Bone' project, she has been investigating whether blueberries may be an appropriate dietary alternative to conventional medicines that prevent bone loss in post-menopausal women.



Q&A

What was your primary motivation for the 'Berries and Bone' project?

I am an expert in mineral metabolism, bioavailability, and function. Early in my career, I studied the trace minerals iron, zinc, and selenium. After 1990, I focused on calcium. Over 99% of calcium in the body is in bone and it is the dominant mineral in bone mineral. I began studies to determine optimal calcium intakes for building peak bone mass in girls and boys of different race and ethnicity. That work led to the recommendations for calcium intake in adolescents in North America. Building peak bone mass is an important strategy to preventing fracture while young, but even more important later in life. Almost 80% of fractures occur in women, so osteoporosis has largely been considered a women's disease. Working in this area of chronic disease for three decades made me sensitive to the under-study of women's chronic diseases generally. So, I started a Global Women's Health Institute at Purdue in 2012 to stimulate research and training in women's diseases, especially osteoporosis, women's cancers, neurodegeneration, and wellness using the high science and engineering strengths of Purdue.

I am interested in many bioactive sources and functional foods. I have had the most success getting funding for blueberries to lower risk of osteoporosis to date. I am also pursuing work with plums. Until we know the bioactive compounds in each and their mechanism of action, we will not know if several fruits can be interchangeable in health benefits or if there are advantages to one over the other. And it isn't as simple as blueberries as a whole. With 1200 different varieties of blueberries, I expect that some will have greater health benefits than others.

Did you find there were benefits to working in such an interdisciplinary team?

Always. In trying to solve the complex problems of today, interdisciplinary research teams are imperative. My collaborators can bring different perspectives as well as a different knowledge base. As a scientist, networking allows you to reach out to others working in related fields and it also helps build

long-term working relationships that really benefit your work.

Could your results be useful in treating bone-related conditions in men as well as women?

This is an interesting avenue for us to explore. Our animal studies show sex differences in the skeleton so we will be evaluating sex differences in response to feeding blueberries in mice. Men do not have the rapid loss of bone that women have with the menopause. Bone loss in men is associated with a more gradual loss of oestrogen as with women more than five years postmenopausal. Thus, we have thought that osteoporosis in men occurs at a more advanced age than in women. Recent statistics show that life expectancy in men is increasing at a faster rate than in women so we need to consider bone health for men more seriously.

Would including polyphenol-rich foods in one's diet from a younger (pre-menopausal) age make preventing age-related bone loss even more effective?

Animal studies show that they are effective in multiple life stages. Generally, it is thought that building higher peak bone mass during growth has the greatest ability to reduce fracture later in life. Bone mass is more stable from about 30 years old to menopause. In animal models, blueberries have been shown to reduce the rapid bone loss with the loss of oestrogen at menopause so this would be a particularly good time to eat plenty of berries and plums. Polyphenol-rich fruits also increase bone formation after the rapid loss of bone with menopause, but this is never as effective as preventing the bone loss in the first place.

What sort of quantities of blueberries do you expect would be beneficial to health?

Unfortunately, we don't know this exactly. We are planning to test this in the future so that we are able to give some specific advice about how many blueberries to eat to prevent age-related bone loss. There is a practical limit to how many blueberries can feasibly be incorporated into the diet. We hope that benefits occur at achievable doses for the general population.

Although not usually life threatening, the number of bone fractures experienced by people in the US exceeds those of cancer, heart attacks and strokes combined. Fractures are more likely in those who have weaker bones as a result of conditions like osteoporosis, which can be treated but currently has no cure. Following the menopause or an ovariectomy (removal of the ovaries), the amount of oestrogen in a woman's body dramatically reduces. This causes the accumulation of reactive oxygen species (ROS) in the body, which, as the name suggests, are highly reactive, and can cause deterioration of the bones.

Previous treatments have included oestrogen therapy (also known as HRT), but this has been shown to incur adverse side effects. The team at Purdue has been trying to identify alternative ways of preventing bone loss in women after this drop-off in oestrogen levels, that do not involve having to take medication. Weaver's hypothesis is that blueberries can help the immune system defend against bone loss.

To test this, the team selected several blueberry strains, trying to choose varieties that were as different from each other as possible, to find out whether the different chemical properties of these berries had an effect on the clinical outcome. So far, they have had some promising results from animal models and hope to find the most effective variety of blueberry for the prevention of bone loss in humans.

WHAT'S SO SPECIAL ABOUT BLUEBERRIES?

Blueberries contain bioactive compounds called polyphenols. According to the US National Institutes of Health, 'bioactive compounds are constituents in foods or dietary supplements, other than those needed to meet basic human nutritional needs, which are responsible for changes in health status'. Polyphenolic compounds are known to reduce bone loss by helping to modulate cell-signalling pathways that cause oxidative stress and inflammation, both factors that affect bone formation and loss.

IT'S THE TRANSCRIPTION THAT COUNTS

Nrf2 is a protein called a transcription factor, that binds to select sections of genetic code and controls the rate of transcription of specific sequences of information. This means that Nrf2 can stimulate the expression of certain genes that can detoxify ROS.

Following the sharp reduction in oestrogen formation that occurs post-menopause, inflammatory processes become more active, and this causes an increase in bone resorption. This is a process whereby cells called osteoclasts break down bone and release the constituent parts, such as calcium, into the blood.

Nrf2 plays a role in controlling inflammation, but the exact mechanisms by which it works, and the way in which it is modulated by blueberry phenolic compounds, are unknown. However, its role in detoxifying ROS has been quantified: Nrf2 binds to antioxidant response elements (AREs), which stimulate the transcription of antioxidant enzymes that protect against the damaging effects of ROS.

Phenolic compounds also inhibit the transcription factor NFκB, which stimulates the expression of genes that prevent bone formation. NFκB increases the activity of osteoclasts, which break down and resorb bone material, and suppresses the activity of osteoblasts, which are responsible for bone formation. Therefore, suppressing NFκB causes osteoblasts to form more new bone material and retain calcium better, while the activity of osteoclasts is reduced.

GUT FEELING

Microbiota in the gut are also likely implicated in the phenol-induced reduction in bone loss. Oestrogen deficiency changes the make-up of microbiotic communities in the gut, which are essential for health. Those with higher gut microbiotic diversity generally have lower rates of inflammation. Gut inflammation is linked to bone loss, and of course the loss of oestrogen causes the accumulation of ROS, and increases inflammation.

The benefits of phenolic compounds are not merely incurred by the products themselves. They also arise as a result of the interaction between polyphenols and gut microflora. Bacteria facilitate the uptake and metabolism of phenolic compounds. These interactions and processes in the gut are an important



part of the health outcomes that bioactive compounds like polyphenols provide.

AN INTERDISCIPLINARY APPROACH

The 'Berries and Bone' project, funded by the NIH National Center for Complimentary and Integrative Health, involves numerous different approaches and facets, and the testing of their hypothesis employs many different techniques and disciplines, including a clinical trial, isotopic tracer

analysis, bioactive activity analysis, epigenetics, cell culture and animal studies, nutrition and statistical analysis. As a result, Weaver collaborates with researchers at various institutions, such as Teresito Bellido, David Burr and Munro Peacock at the Indiana University School of Medicine, Mario Ferruzzi and Mary Ann Lila at North Carolina State University, as well as George McCabe, her colleague at Purdue.

CAN DIET REPLACE TREATMENT AS A PRIMARY PREVENTION FOR CHRONIC DISEASE?

The Purdue team has shown that administration of natural antioxidant-rich products, such as blueberries, reduced bone loss in mice. They now need to translate these findings into the effects on humans. They have used animal models to

find a dosage that can stimulate a positive effect, and will apply these findings to upcoming clinical trials following their approval.

Weaver's work suggests that prevention of some diseases, such as osteoporosis in older women, is achievable with dietary measures. As the adage goes, prevention is better than cure – both in terms of patient health outcomes, and the financial burden on healthcare services. Purdue is at the forefront of the drive to understand how berries can benefit bone formation. Encouraging patients to include phenolic berries in their diets could greatly lower their risk of developing problems related to bone loss or low bone mass, and could be an attractive alternative to conventional medicine-based treatment.

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Detail

RESEARCH OBJECTIVES

Professor Connie Weaver and her team are studying the most effective blueberry line for improving bone density and strength and preventing bone loss in postmenopausal women and animal models. Understanding the mechanism by which berries ameliorate menopause-induced and age-related bone loss is one of the most compelling avenues to pursue in natural products research.

COLLABORATORS

- George McCabe, Purdue University
- Teresito Bellido, Indiana University School of Medicine
- David Burr, Indiana University School of Medicine
- Munro Peacock, Indiana University School of Medicine
- Mario Ferruzzi, North Carolina State University
- Mary Ann Lila, North Carolina State University

BIO

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