An anti-osteoporosis recipe

With incidence of osteoporosis on the rise, **Professor Brenda Smith** is searching for novel treatment strategies among plant-based foods. Here, she provides an overview of the most promising candidates on the menu

How has your initial interest in nutrition and chronic disease developed into your current lines of investigation?

I have always been drawn to the study of chronic disease prevention based on the fundamental belief that prevention is the point at which we could have the greatest impact on the health of individuals, as well as populations. This idea is what initially drew me to the field of exercise physiology. After time in the field, I began to develop a strong interest in the role of nutrition in chronic disease – and my background as an exercise physiologist and training in nutritional sciences converged in the study of bone health. The initial premise was quite simple: the need to understand how dietary components, in conjunction with appropriate weight-bearing physical activity, could be used to develop effective prevention and treatment strategies for osteoporosis.

Over time, advances in the field of bone biology have highlighted the importance of the immune system in regulating bone metabolism and how its dysregulation – brought about by menopause, ageing and chronic inflammatory conditions – contributes to bone loss. This progress has actually resulted in the development of a new scientific discipline – osteoimmunology.

I became very intrigued with understanding how dietary components modulate the immune response, particularly when considering the immune system's role in most chronic diseases. The advances in osteoimmunology, combined with my interest in immunonutrition, led to my team's current line of investigation in understanding how dietary factors that alter the immune system impact skeletal integrity.

Can you provide an overview of osteoporosis and its current treatments?

Musculoskeletal diseases such as osteoporosis and osteoarthritis are the most common causes of long-term pain and physical disability. It is estimated that by 2020, 50 per cent of women and 20 per cent of men over 50 years of age will experience an osteoporotic-related fracture. In the US, there are currently several Food and Drug Administration (FDA)-approved pharmacological agents targeting the suppression of osteoclast activity, which reduce the rate of bone loss. Only one available anabolic agent can restore bone, but it is generally cost-prohibitive. The problem with these current therapies is the side effects, and patient compliance has been poor. More effective and affordable prevention strategies and treatment options with fewer side effects are necessary to meet this growing problem.

What promising plant-based foods are you studying in an effort to find alternative therapies for osteoporosis?

The primary focus of our work has been on plums (*Prunus domestica L.*) and their bioactive components. The dried plum is of particular interest because it is a rich source of phenolic compounds that have both antioxidant and immunomodulating properties. Furthermore, dietary supplementation with dried plum has been shown to not only prevent bone loss in a similar manner to other food sources of phenolic compounds, but also to have anabolic effects such as the capacity to restore bone mass.

More recently, we have also started to study the effects of supplementing the diet with tart cherry – another food rich in phenolics. They are of particular interest to our work because their phenolic compound profile is very similar to that of dried plum. Preliminary results with tart cherry and its effects on bone appear to be very promising.

Which research strategies are you employing in order to understand how bone metabolism is altered and identify the bioactive components in dried plum?

There is a need to identify the bioactive components in dried plums and understand their mechanisms of action. We are capitalising on single cell and co-culture systems, animal models and high throughput assays to study the various compounds and their influence on bone metabolism. This process can be challenging, considering the number of potential bioactive components and the possibility that the effects may be mediated directly on bone cells or indirectly via another physiological system (eg. the immune system). Despite this, we are making progress and gaining a greater understanding of how plant-based foods rich in phenolic compounds mediate their health benefits.

How far away are your laboratory-based findings from being translated into the clinic?

Understanding what component of dried plum is responsible for the positive effects on bone, and the mechanisms by which this occurs, is important in order to optimise the dosing and efficacy prior to the findings being translated into clinical practice. However, preliminary clinical trials by investigators at Florida State University and San Diego State University have provided positive evidence that postmenopausal bone loss is at least slowed with dietary supplementation (100 g per day) of dried plum. Further research is necessary to understand the bioactive components in plum so that reasonable doses with optimal effect can be explored.

Bioactive components and bones

At **Oklahoma State University**, a team of nutritional scientists is exploring the ways that certain bioactive components can impact bone metabolism with the goal of translating their findings to the clinic

OSTEOPOROSIS IS ONE of the most costly and debilitating diseases associated with ageing – and it is on the rise. Annually, osteoporosis causes more than 8.9 million fractures worldwide, which translates to an associated fracture occurring every three seconds. Current figures predict that, by 2050, the worldwide incidence of hip fracture in men is projected to increase by 310 per cent and 240 per cent in women. What is more, as life expectancies continue to climb, disease incidence is expected to grow.

Although there have been significant developments in osteoporosis treatments over recent years, existing therapies remain a challenge due to poor patient compliance and the common risk of side effects. Of the therapies currently approved by the US Food and Drug Administration (FDA), all but one are anti-resorptive – meaning they primarily reduce bone loss, but do not restore bone. Although one anabolic pharmacological agent (teriparatide) exists that restores bone in patients with established osteoporosis, it requires a daily injection and is cost-prohibitive to many patients.

If researchers were to find a means to both prevent and reverse the disease that was effective, affordable and had few or no side effects, the impact would be significant, to say the least. At Oklahoma State University, a group of scientists based in the College of Human Sciences and led by Professor Brenda Smith is aiming to do exactly this.

ANSWERS ON A PLATE

Smith's team aims to identify plant-based foods – and the bioactive components contained therein – that could be incorporated into strategies developed to prevent and/or treat osteoporosis. Their overarching goal is to apply their findings to develop new therapeutic targets, dietary recommendations or supplements.

To achieve this endpoint, the group employs a highly multidisciplinary approach, and the study is a collaborative effort between scientists with specialised skills and expertise from a broad range of disciplines. With a combined knowledge base in analytical chemistry, nutrigenomics, natural products and molecular plant biology, the researchers are adequately equipped to see this research translated to practice.

A DRIED PLUM PRESCRIPTION

So far, the foodstuff that has excited Smith's team the most is the dried plum (*Prunus domestica L.*). Previous research, conducted both by this group and others, has demonstrated that dried plum has the capacity to not only prevent but also reverse bone loss in animal models of postmenopausal and age-related bone loss. Although a number of other natural products that demonstrate osteoprotective properties have been identified, dried plum has been by far the most promising. If this finding is to be translated to the clinic, however, the bioactive components in dried plum and the mechanisms through which they alter bone metabolism must be elucidated.

At present, the scientists hypothesise that it is the abundant phenolic compounds in dried plum that are at least in part responsible for the therapeutic effect, through the regulation of osteoblast differentiation and activity, and inhibition of osteoclastogenesis. To test this hypothesis, Smith and her colleagues are using a reductionist approach involving murine and human cell models to determine how different types of phenolics from dried plum affect osteoblast and osteoclast differentiation and activity. Already, they have confirmed that osteoclast activity is downregulated in response to plum's phenolic compounds. "We continue to work out the details of the signalling pathways through which a biphasic effect on osteoblast activity is mediated," Smith reveals.

The team aims to identify plant-based foods – and the bioactive components contained therein – that could be incorporated into strategies developed to prevent and/or treat osteoporosis

BIOACTIVE COMPONENTS IN FOODS AND BONE HEALTH

OBJECTIVES

- To explore the osteoprotective effects of plant-based foods with a goal of translating findings into osteoporosis prevention and treatment strategies
- To investigate the negative effects that type 2 diabetes has on bone health so that viable treatment options can be identified

KEY COLLABORATORS

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BRENDA SMITH initially trained in exercise physiology, before undertaking a PhD in Human Nutrition at Oklahoma State University and subsequently a postdoctoral fellowship in Nutrition and Bone Metabolism. She currently holds the John and Sue Taylor Professorship at the University and received the Regent's Distinguished Research Award in 2009 for her work.

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IMPROVED BONE HEALTH FOR DIABETICS

Another application of Smith's efforts to understand how diet-related factors influence bone health is focused on type 2 diabetes. Evidence suggests that this condition negatively impacts bone metabolism and consequently bone quality. It has been shown, for example, that an individual's risk of osteoporotic fracture almost doubles five to 10 years after the diagnosis of type 2 diabetes. With the prevalence of this disease on the rise, combined with rapidly ageing societies around the world, it seems probable that cases of osteoporotic fracture will also increase.

In light of this, the Smith group is conducting research aimed at characterising the pathophysiology of compromised skeletal health in type 2 diabetes – an especially pertinent goal as Oklahoma has one of the highest rates of this disease in the US. Research efforts range from investigating the effects of type 2 diabetes on bone metabolism among a cohort of Native American women, to exploring the mechanism by which alterations in the immune system and glucose homeostasis effect bone metabolism and lead to compromised bone biomechanical properties.

Such insights will be vital to pinpoint appropriate therapies – some of which may involve the use of the bioactive components identified by the group.

The researchers are also investigating the therapeutic potential of dried plum from a range of other angles. These studies include investigating the differences in therapeutic effects of different plum cultivars, and discovering that dietary supplementation with dried plum has potent immunomodulating properties that suppress T cell and monocyte activation in cases of ovarian hormone deficiency (which are known to play a role in postmenopausal bone loss).

CHERRY ON TOP

Moreover, the Smith Lab is not focusing all of its research efforts on dried plum; another candidate of note is the tart cherry. The team was prompted to pursue research in this regard due to its similarity to dried plum in terms of polyphenolic profile. As such, a project is currently underway to determine to what extent consumption of tart cherries can prevent bone loss and alter bone metabolism.

It is this last challenge – understanding how these phenolic-rich, plant-based foods influence bone health – that is key to the group's mission. "While we have gained insights into biphasic effect on bone turnover over the last five years, it is still not clear how these effects are mediated and what causes the shift to occur in the promotion of bone formation," Smith expands. "Furthermore, understanding the bioactive components involved may not only provide a new cost-effective prevention or treatment strategy for osteoporosis, but also allow us to identify new therapeutic targets."

BEYOND BONES

For the moment, this Oklahoma group will continue in its efforts to identify and understand how the bioactive components of select foods can positively impact osteoporosis. It is likely, therefore, that their findings will have applications beyond osteoporosis. "We have recently begun to investigate how phenolic compounds may impact the gut microbiota and, ultimately, the gut mucosal immune system," Smith reveals. "These studies have potential implications for our understanding of the health benefits offered by plant-based foods, not only in osteoporosis but potentially in many chronic diseases."