Study proposes isotope analysis for earlier detection of bone loss

May 28 2012

This image of the Caduceus, a century-old symbol of medicine, merged with a rock hammer, the traditional symbol of geology, illustrates the research by scientists at Arizona State University and NASA who are developing a new approach to the medical challenge of detecting bone loss by applying a technique that originated in the Earth sciences. Credit: Susan Selkirk/School of Earth and Space Exploration/Arizona State University

Are your bones getting stronger or weaker? Right now, it's hard to know. Scientists at Arizona State University and NASA are taking on this medical challenge by developing and applying a technique that originated in the Earth sciences. In a new study, this technique was more sensitive in detecting bone loss than the X-ray method used today, with less risk to patients. Eventually, it may find use in clinical settings, and could pave the way for additional innovative biosignatures to detect disease.

"Osteoporosis, a disease in which bones grow weaker, threatens more than half of Americans over age 50," explained Ariel Anbar, a professor in ASU's Department of Chemistry and Biochemistry and the School of Earth and Space Exploration, and senior author of the study.

"Bone loss also occurs in a number of cancers in their advanced stages. By the time these changes can be detected by X-rays, as a loss of bone density, significant damage has already occurred," Anbar said. "Also, X-rays aren't risk-free. We think there might be a better way."

With the new technique, bone loss is detected by carefully analyzing the isotopes of the chemical element calcium that are naturally present in urine. Isotopes are atoms of an element that differ in their masses. Patients do not need to ingest any artificial tracers and are not exposed to any radiation, so there is virtually no risk, the authors noted.

The findings are presented in a paper published in the online Early Edition of the Proceedings of the National Academy of Sciences (*PNAS*) the week of May 28. It is titled "Rapidly assessing changes in bone mineral balance using natural stable calcium isotopes."

"The paper suggests an exciting new approach to the problem," said Dr. Rafael Fonseca, chair of the Department of Medicine at the Mayo Clinic in Arizona, and a specialist in the bone-destroying disease multiple myeloma. Fonseca was not associated with the study but is partnering with the ASU team on collaborative research based on the findings.

"Right now, pain is usually the first indication that cancer is affecting bones. If we could detect it earlier by an analysis of urine or blood in high-risk patients, it could significantly improve their care," Fonseca said.

The new technique makes use of a fact well known to Earth scientists, but seldom used in biomedicine: Different isotopes of a chemical element can react at slightly different rates. When bones form, the lighter isotopes of calcium enter bone a little faster than the heavier isotopes. That difference, called "isotope fractionation," is the key.

"Instead of isotopes of calcium, think about jelly beans," explained Jennifer Morgan, lead author of the study. "We all have our favorite. Imagine a huge pile of jelly beans with equal amounts of six different kinds. You get to make your own personal pile, picking out the ones you want. Maybe you pick two black ones for every one of another color because you really like licorice. It's easy to see that your pile will wind up with more black jelly beans than any other color. Therefore, the ratio of black to red or black to green will be higher in your pile than in the big one. That's similar to what happens with calcium isotopes when bones form. Bone favors lighter calcium isotopes and picks them over the heavier ones."

Other factors, especially bone destruction, also come into play, making the human body more complicated than the jelly bean analogy. But 15 years ago, corresponding author Joseph Skulan, now an adjunct professor at ASU, combined all the factors into a mathematical model that predicted that calcium isotope ratios in blood and urine should be extremely sensitive to bone mineral balance.

"Bone is continuously being formed and destroyed," Skulan explained. "In healthy, active humans, these processes are in balance. But if a disease throws the balance off then you ought to see a shift in the calcium isotope ratios."

The predicted effect on calcium isotopes is very small, but can be measured using sensitive mass spectrometry methods developed by Morgan as part of her doctoral work with Anbar, Skulan and co-author Gwyneth Gordon, an associate research scientist in the W.M. Keck Foundation Laboratory for Environmental Biogeochemistry at ASU. Co-author Stephen Romaniello, currently a doctoral student with Anbar at ASU, contributed an updated mathematical model.

The new study, funded by NASA, examined calcium isotopes in the urine of a dozen healthy subjects confined to bed ("bed rest") for 30 days at the University of Texas Medical Branch at Galveston's Institute for Translational Sciences–Clinical Research Center. Whenever a person lies down, the weight-bearing bones of the body, such as those in the spine and leg, are relieved of their burden, a condition known as "skeletal unloading". With skeletal unloading, bones start to deteriorate due to increased destruction. Extended periods of bed rest induce bone loss similar to that experienced by osteoporosis patients, and astronauts.

"NASA conducts these studies because astronauts in microgravity experience skeletal unloading and suffer bone loss," said co-author Scott M. Smith, NASA nutritionist. "It's one of the major problems in human spaceflight, and we need to find better ways to monitor and counteract it. But the methods used to detect the effects of skeletal unloading in astronauts are also relevant to general medicine."

Lab analysis of the subjects' urine samples at ASU revealed that the new technique can detect bone loss after as little as one week of bed rest, long before changes in bone density are detectable by the conventional approach, dual-energy X-ray absorptiometry (DEXA).

Importantly, it is the only method, other than DEXA, that directly measures net bone loss.

"What we really want to know is whether the amount of bone in the body is increasing or decreasing", said Morgan.

Calcium isotope measurements seem poised to assume an important role in detecting bone disease – in space, and on Earth. The team is working now to evaluate the technique in samples from cancer patients.

"This is a 'proof-of-concept' paper," explained Anbar "We showed that the concept works as expected in healthy people in a well-defined experiment. The next step is to see if it works as expected in patients with bone-altering diseases. That would open the door to clinical applications."

However, the concept extends even beyond bone and calcium, the authors noted. Many diseases may cause subtle changes in element isotope abundances, or in the concentrations of elements. These sorts of signatures have not been systematically explored in the development of biosignatures of cancers and other diseases.

"The concept of inorganic signatures represents a new and exciting approach to diagnosing, treating and monitoring complex diseases such as cancer," stated Anna Barker, director of Transformative Healthcare Networks and co-director of the Complex Adaptive Systems Initiative in the Office of Knowledge Enterprise Development at ASU. Barker, who came to ASU after being deputy director of the National Cancer Institute, emphasized the simplicity of the approach compared to the challenges of deciphering complex genome-derived data, adding "there is an opportunity to create an entirely new generation of diagnostics for cancer and other diseases."

Provided by Arizona State University