

Fiscal Year:	FY 2012	Task Last Updated:	FY 05/08/2012
PI Name:	Anbar, Ariel Ph.D.		
Project Title:	Rapid measurements of bone loss using tracer-less calcium isotope analysis of blood and urine		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
Program/Discipline-- Element/Subdiscipline:	HUMAN RESEARCH--Biomedical countermeasures		
Joint Agency Name:	TechPort:	Yes	
Human Research Program Elements:	(1) HHC :Human Health Countermeasures		
Human Research Program Risks:	(1) Bone Fracture :Risk of Bone Fracture due to Spaceflight-induced Changes to Bone (2) Osteo :Risk Of Early Onset Osteoporosis Due To Spaceflight		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	GROUND	Solicitation / Funding Source:	2007 Crew Health NNJ07ZSA002N
Start Date:	05/20/2008	End Date:	03/19/2013
No. of Post Docs:		No. of PhD Degrees:	
No. of PhD Candidates:	1	No. of Master' Degrees:	
No. of Master's Candidates:		No. of Bachelor's Degrees:	
No. of Bachelor's Candidates:	1	Monitoring Center:	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: Received extension to 3/19/2013 per NSSC (Ed., 5/8/2012) NOTE: Received extension to 5/19/2012 per C. Guidry/JSC and NSSC [Ed. 3/2/2011]		
Key Personnel Changes/Previous PI:	None		
COI Name (Institution):	Skulan, Jospheh (University of Wisconsin-Madison Geology Museum) Smith, Scott (Human Adaptation and Countermeasures Division) Bullen, Thomas (USGS)		
Grant/Contract No.:	NNX08AQ36G		
Performance Goal No.:			
Performance Goal Text:			

<p>Task Description:</p>	<p>We propose to develop a method to rapidly detect changes in bone mineral balance by measuring the natural (i.e., tracer-less) isotope composition of calcium in blood and/or urine. This method would provide a way to detect incipient bone loss before changes in bone density are detectable by conventional X-Ray methods.</p> <p>The resorption of bone when astronauts are exposed to microgravity is a major challenge for NASA's plans for human exploration of the Moon and Mars. Our proposed technique would be immediately valuable in ground-based studies of countermeasure strategies, accelerating the pace of discovery of countermeasures to bone loss. In the long run, flight-qualified versions of mass spectrometric or other systems for Ca isotope characterization could accompany astronauts on long-duration missions.</p> <p>Precise measurements of the calcium isotope composition in blood or urine provide information about bone mineral balance because the isotopic composition of calcium in human soft tissues is naturally affected by the relative rates of bone formation and resorption. Specifically, lighter calcium isotopes are preferentially incorporated into bone during formation. Because of the short residence time of calcium in soft tissues, calcium isotope ratios should change rapidly in response to changes bone gain or loss. These changes, while small, can be measured by multiple collector inductively coupled plasma mass spectrometry (MC-ICP-MS) or thermal ionization mass spectrometry (TIMS).</p> <p>The proposal team recently demonstrated the promise of this method in a published pilot study in which we measured calcium isotopes in a small suite of urine samples from a bed rest study. Here, we propose an expanded examination of bed rest samples, involving a larger number of subjects, measurements of blood and dietary samples as well as urine, and daily or even sub-daily sampling. This research would address critical questions unresolved by the pilot study.</p>
<p>Rationale for HRP Directed Research:</p>	<p>We are developing a technique that uses analyses of natural variations in the calcium isotope composition of urine, blood and other biological materials to measure changes in bone mineral balance. The focus of this research is detecting bone loss resulting from skeletal unloading in the microgravity of space, but our technique is equally applicable wherever disruptions in bone mineral balance are an issue. Ca isotope analysis may provide a way of detecting incipient bone loss before it has produced any measurable change in bone mineral density, and long before it has progressed to osteopenia or osteoporosis. Because soft tissue Ca isotope composition changes very rapidly in response to changes in bone mineral balance, our technique also may be used to rapidly assess the effectiveness of treatments designed to alter bone mineral balance, greatly accelerating the pace of discovery of new treatments for metabolic bone diseases such as osteoporosis.</p>
<p>Research Impact/Earth Benefits:</p>	<p>During the past year, we encountered significant delays due to multiple, unexpected equipment failures on our high precision mass spectrometer. These problems began in June, 2011 and were resolved through the replacement of several major components of our mass spectroscopic system (detectors, computer system, and several electronics boards). The final repair is happening this month. For this reason few new analyses were completed during this project year, and we slowed our pace of spending, leading us to request a one-year, no cost extension. Nevertheless, we have made significant progress on several fronts:</p> <ol style="list-style-type: none"> 1. Most of the blood and food samples collected during the 30 day bed rest study have been purified and are ready for analysis. As discussed in last year's progress report, sample purification is the most time consuming step in Ca isotope analysis of biological samples. New chemical techniques needed to be devised in order to reduce Sr and K concentrations to the extremely low levels required for mass spectrometric analysis. These techniques were developed in the earlier project years, and published in Summer, 2011 (Morgan et al., 2011). They are also included in a patent claim being pursued by Arizona State University. 2. Largely through the efforts of Steven Romaniello, a PhD student in Dr. Anbar's lab, we have made significant advances in the theoretical understanding of Ca isotope fractionation in the human body, and how this fractionation affects the urinary Ca isotope response to changes in bone mineral balance. Mr. Romaniello has developed a mathematical model that includes the important variables controlling the Ca isotope composition of soft tissue and urine, including the isotope composition of diet, intestinal Ca absorption, bone remodeling rate, and Ca isotope fractionation during bone formation. <p>Importantly, the mathematical model takes into account renal and hepatic Ca isotope fractionation. Until now, renal Ca isotope fractionation has been the major outstanding issue in biological Ca isotope research, and a potential problem for the application of Ca isotope analysis to the measure of bone mineral balance. It now is clear that renal fractionation can be adequately accounted for in the model. Moreover, given the likely value of the renal Ca isotope effect, which can be inferred from our own and others' work on humans and animal models, renal fractionation actually increases the sensitivity of Ca isotopes in urine to changes in bone mineral balance.</p> <p>Once the renal isotope effect has been measured with sufficient precision through the analysis of the remaining blood and food samples, the mathematical model will allow us to use changes in urinary Ca isotope composition to make truly quantitative calculations of bone mineral balance.</p> <ol style="list-style-type: none"> 3. Results of our research have been communicated at several major international meetings, including the annual meeting of the Endocrine Society, the American Geophysical Union, and the annual Goldschmidt conference. We have made plans future collaboration with European researchers who have been independently investigating the relationship between urinary Ca isotopes and bone mineral balance. 4. Results of the analysis of approximately 200 urine samples, together with our mathematical model and a detailed discussion of the renal isotope effect, are described in our paper, Rapidly assessing changes in bone mineral balance using natural stable calcium isotopes, which currently is in revision at PNAS. This paper is the most exhaustive treatment to date of Ca isotopes in humans. It demonstrates that Ca isotopes in urine respond to changes in BMB within ten days of the start of bed rest, and the feasibility of using urinary Ca isotopes to quantitatively measure changes in BMB. <p>Future plans: Over the next year we will finish the analysis of blood and diet samples collected during the bed rest study, and use these new data to refine our mathematical model. In particular, we will have multiple simultaneous measures of the Ca isotope composition of blood and urine from the same subjects. These data will allow us to quantify the renal fractionation factor, and shed light on the exact mechanism of renal Ca isotope fractionation. We anticipate writing at least two major papers presenting our results.</p>
<p>Task Progress:</p>	

Bibliography Type:	Description: (Last Updated: 10/09/2019)
Abstracts for Journals and Proceedings	Morgan JL, Gordon GW, Romaniello SJ, Skulan JL, Smith SM, Anbar AD. "Rapidly assessing changes in bone mineral balance using natural stable calcium isotopes." Goldschmidt 2011, Prague, Czech Republic, August 14-19, 2011. Mineralogical Magazine, 2011 Jun;75(3):1501. Search PDF at http://minmag.geoscienceworld.org/content/75/3/1374.full.pdf+html , Jun-2011
Abstracts for Journals and Proceedings	Morgan JL, Gordon GW, Skulan JL, Anbar AD. "Rapidly Assessing Changes in Bone Mineral Balance Using Natural Stable Ca Isotope Composition of Urine." Presented at ENDO 2011, Boston, MA, June 4-7, 2011. Endocrine Reviews, 2011 Jun;32(3, Meeting Abstracts):2-107. , Jun-2011
Abstracts for Journals and Proceedings	Skulan JL, Gordon GW, Morgan J, Rominello SJ, Smith SM, Anbar AD. "Natural Ca isotope composition of urine as a rapid measure of bone mineral balance." Presented at 2011 Fall Meeting of the American Geophysical Union Conference, San Francisco, CA, December 5-9, 2011. AGU 2011 Fall Meeting Abstract number B54D-08. , Dec-2011
Articles in Peer-reviewed Journals	Morgan JL, Gordon GW, Arrua RC, Skulan JL, Anbar AD, Bullen TD. "High-precision measurement of variations in calcium isotope ratios in urine by multiple collector inductively coupled plasma mass spectrometry." Analytical Chemistry, 2011 Sep 15;83(18):6956-62. Epub 2011 Aug 18. http://dx.doi.org/10.1021/ac200361t ; PubMed PMID: 21740001 , Sep-2011